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1. APPLICATIONS

1.1. *Small Molecules*

Water and Solvation

Enhancement of the Thermal Polarization of Water via Heat Flux and Dipole Moment Dynamic Correlations

Jeff Armstrong, Anders Lervik[Imperial College London], and Fernando Bresme

J. Phys. Chem. B., **117**, 14817–14826, 2013**.**

This polarization effect can be significant for temperature gradients that can be achieved at micro and nanoscales. In this paper we investigate the dependence of the polarization response of liquid and supercritical water at different thermodynamic conditions using both equilibrium and nonequilibrium molecular dynamics simulations for the extended point charge water model. We find that the thermal polarization features a nonmonotonic behavior with temperature, reaching a maximum response at specific thermodynamic states.

SPAM: A Simple Approach for Profiling Bound Water Molecules

Guanglei Cui[GlaxoSmithKline Pharmaceuticals], Jason M. Swails, and Eric S. Manas

J. Chem. Theor. and Comp, **9**, 5539–5549, 2013.

A method that identifies the hydration shell structure of proteins and estimates the relative free energies of water molecules within that hydration shell is described. The method, which we call "SPAM" (*maps* spelled in reverse), utilizes explicit solvent molecular dynamics (MD) simulations to capture discrete hydration sites at the water–protein interface and computes a local free energy measure from the distribution of interaction energies between water and the environment at a specific site.

MMCC Results

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Medicinal Chemistry and Drug Design

P1 and P1′ *para*-fluoro phenyl groups show enhanced binding and favorable predicted pharmacological properties: Structure-based virtual screening of extended lopinavir analogs against multi-drug resistant HIV-1 protease

Ravikiran S. Yedidi, Zhigang Liu, Iulia A. Kovari, Patrick M. Woster, Ladislau C. Kovari[Wayne State University]

J. Mol.Graph. and Mod., **47,** 18-24, 2014.

Crystal structure of multidrug-resistant (MDR) clinical isolate 769, human immunodeficiency virus type-1 (HIV-1) protease in complex with lopinavir (LPV) (PDB ID: 1RV7) showed altered binding orientation of LPV in the expanded active site cavity, causing loss of contacts and decrease in potency. In the current study, with a goal to restore the lost contacts, three libraries of LPV analogs containing extended P1 and/or P1′ phenylgroups were designed and docked into the expanded active site cavity of the MDR769 HIV-1 protease. The compounds were then ranked based on three criteria: binding affinity, overall binding profile and predicted pharmacological properties.

Theoretical studies of the interaction between influenza virus hemagglutinin and its small molecule ligands

Deshou Song, Hanhong Xu[South China Agricultural University], Shuwen Liu

J. Mol.Mod., **19,** 5561-5568, 2013.

Hemagglutinin (HA) is a membrane protein present on the influenza viral envelope. It is responsible for molecular recognition between the viral particle and the host cell, as well as fusion of the viral envelope to the endosome bilayer. In order to compare their different inhibitory activities and shed light on drug design targeting the HA protein, we conducted a variety of theoretical calculations, including docking, molecular dynamics simulations, free energy calculations, as well as quantum calculations to investigate interactions between these two ligands and the HA protein.

In-silico screening of cancer associated mutation on PLK1 protein and its structural consequences

Balu Kamaraj, Vidya Rajendran, Rao Sethumadhavan, Rituraj Purohit

J. Mol.Mod., **19,** 5587-5599, 2013.

The Polo-like kinases (Plks) are a conserved subfamily of serine-threonine protein kinases that have significant roles in cell proliferation. The serine/threonine protein kinases or polo-like kinase 1 (PLK1) exist in centrosome during interphase and is an important regulatory enzyme in cell cycle progression during M phase. In this analysis we implemented a computational approach to filter the most deleterious and cancer associated mutation on PLK1 protein. We found W414F as the most deleterious and cancer associated by Polyphen 2.0, SIFT, I-mutant 3.0, PANTHER, PhD-SNP, SNP&GO, Mutpred and Dr Cancer tools.

Para-(benzoyl)-phenylalanine as a potential inhibitor against LpxC of Leptospira spp.: homology modeling, docking, and molecular dynamics study

Dibyabhaba Pradhan, Vani Priyadarshini, Manne Munikumar, Sandeep Swargam, Amineni Umamaheswari & Aparna Bitla[SVIMS University]

J. Biomol. Stru. and Dyn., 31, 171-185,*2013.*

Leptospira interrogans, a Gram-negative bacterial pathogen is the main cause of human leptospirosis. Lipid A is a highly immunoreactive endotoxic center of lipopolysaccharide (LPS) that anchors LPS into the outer membrane of Leptospira. Discovery of compounds inhibiting lipid-A biosynthetic pathway would be promising for dissolving the structural integrity of membrane leading to cell lysis and death of Leptospira. LpxC, a unique enzyme of lipid-A biosynthetic pathway was identified as common drug target of Leptospira.

Medicinal Chemistry and Drug Design (Cont'd)

Probing the structure of Mycobacterium tuberculosis MbtA: model validation using molecular dynamics simulations and docking studies

Lakshmi Maganti, Open Source Drug Discovery Consortium & Nanda Ghoshal[CSIR-Indian Institute of Chemical Biology]

J. Biomol. Stru. and Dyn., 31, 273-288,*2013.*

Multidrug resistance capacity of Mycobacterium tuberculosis demands urgent need for developing new antitubercular drugs. The present work is on M. tuberculosis-MbtA, an enzyme involved in the biosynthesis of siderophores, having a critical role in bacterial growth and virulence. The molecular models of both holo and apo forms of M. tuberculosis-MbtA have been constructed and validated. A docking study with a series of 42 5′-O-[N-(salicyl) sulfamoyl] adenosine derivatives, using GOLD software, revealed significant correlation (R2 = 0.8611) between Goldscore and the reported binding affinity data. Further, binding energies of the docked poses were calculated and compared with the observed binding affinities (R2 = 0.901).

Structure–Activity Relationships and Identification of Optmized CC-Chemokine Receptor CCR1, 5, and 8 Metal-Ion Chelators

Alexander Chalikiopoulos, Stefanie Thiele, Mikkel Malmgaard-Clausen, Patrik Rydberg, Vignir Isberg, Trond Ulven, Thomas M. Frimurer, Mette M. Rosenkilde, and David E. Gloriam [University of Copenhagen,]

J.Chem. Infor. and Mod. **53**, 2863–2873, 2013.

S!

Chemokine receptors are involved in trafficking of leukocytes and represent targets for autoimmune conditions, inflammatory diseases, viral infections, and cancer. We recently published CCR1, CCR8, and CCR5 agonists and positive modulators based on a three metal-ion chelator series: 2,2′-bipyridine, 1,10-phenanthroline, and 2,2′;6′,2″-terpyridine. Here, we have performed an in-depth structure–activity relationship study and tested eight new optimized analogs. Using density functional theory calculations we demonstrate that the chelator zinc affinities depend on how electron-donating and -withdrawing substituents modulate the partial charges of chelating nitrogens.

Molecular Dynamic Simulations of Ocular Tablet Dissolution

Qian Ru, Hala M. Fadda, Chung Li, Daniel Paul, Peng T. Khaw, Steve Brocchini, and Mire Zloh[University of Hertfordshire]

J.Chem. Infor. and Mod. **53**, 3000–3008, 2013.

S!

There is a need to evaluate drug dissolution at the molecular level to determine how the chemical structure of the active may correlate with dissolution in the nonsink conditions of the conjunctival space. We conducted molecular dynamics simulations to study the dissolution process of tablets derived from two drugs that can inhibit fibrosis after GFS, 5-fluorouracil (5-FU) and the matrix metalloprotease inhibitor (MMPi), ilomastat.

Detailed Computational Study of the Active Site of the Hepatitis C Viral RNA Polymerase to Aid Novel Drug Design

Khaled H. Barakat[University of Alberta,], John Law, Alessio Prunotto, Wendy C. Magee, David H. Evans, D. Lorne Tyrrell, Jack Tuszynski, and Michael Houghton

J.Chem. Infor. and Mod. **53**, 3031–3043, 2013.

The hepatitis C virus (HCV) RNA polymerase, NS5B, is a leading target for novel and selective HCV drug design. The enzyme has been the subject of intensive drug discovery aimed at developing direct acting antiviral (DAA) agents that inhibit its activity and hence prevent the virus from replicating its genome. In this study, we focus on one class of NS5B inhibitors, namely nucleos(t)ide mimetics. Forty-one distinct nucleotide structures have been modeled within the active site of NS5B for the six major HCV genotypes.

Medicinal Chemistry and Drug Design (Cont'd)

Fusing Dual-Event Data Sets for *Mycobacterium tuberculosis* Machine Learning Models and Their Evaluation

Sean Ekins[Collaborative Drug Discovery], Joel S. Freundlich, and Robert C. Reynolds

J.Chem. Infor. and Mod. **53**, 3054–3063, 2013.

Multiple large scale phenotypic high-throughput screens against*Mycobacterium tuberculosis* (*Mtb*) have generated dose response data, enabling the generation of machine learning models. These models also incorporated cytotoxicity data and were recently validated with a large external data set. A cheminformatics data-fusion approach followed by Bayesian machine learning, Support Vector Machine, or Recursive Partitioning model development (based on publicly available *Mtb* screening data) was used to compare individual data sets and subsequent combined models.

Improving the Resistance Profile of Hepatitis C NS3/4A Inhibitors: Dynamic Substrate Envelope Guided Design

Ayşegül Özen, Woody Sherman, and Celia A. Schiffer [University of Massachusetts Medical School]

J. Chem. Theor. and Comp, **9**, 5693–5705, 2013.

Drug resistance is a principal concern in the treatment of quickly evolving diseases. The viral protease NS3/4A is a primary drug target for the hepatitis C virus (HCV) and is known to evolve resistance mutations in response to drug therapy. Previously we have developed the "substrate envelope" hypothesis, which posits that inhibitors should be less susceptible to drug resistance if they better mimic the natural substrate molecular recognition features. In this work, we perform MD simulations on four native substrates bound to NS3/4A and discover a clearly conserved dynamic substrate envelope.

High-Throughput Virtual Screening Identifies Novel *N′*-(1-Phenylethylidene)-benzohydrazides as Potent, Specific, and Reversible LSD1 Inhibitors

Venkataswamy Sorna, Emily R. Theisen, Bret Stephens, Steven L. Warner, David J. Bearss, Hariprasad Vankayalapati, and Sunil Sharma[University of Utah]

J.Med.Chem., **56,** 9496–9508, 2013.

S!

Lysine specific demethylase 1 (LSD1) plays an important role in regulating histone lysine methylation at residues K4 and K9 on histone H3 and is an attractive therapeutic target in multiple malignancies. Here we report a structure-based virtual screen of a compound library containing ~2 million small molecular entities. Computational docking and scoring followed by biochemical screening led to the identification of a novel *N′*-(1-phenylethylidene)-benzohydrazide series of LSD1 inhibitors with hits showing biochemical IC_{50}s in the 200–400 nM range. Hit-to-lead optimization and structure–activity relationship studies aided in the discovery of compound **12**, with a K_i of 31 nM.

Quantitative Structure-Activity Relations

Fragment-based strategy for structural optimization in combination with 3D-QSAR

Haoliang Yuan[China Pharmaceutical Universit], Wenting Tai, Shihe Hu, Haichun Liu, Yanmin Zhang, Sihui Yao, Ting Ran, Shuai Lu, Zhipeng Ke, Xiao Xiong, Jinxing Xu, Yadong Chen, Tao Lu

J. Comp. Aided. Mol. Design, **27**, 897-915, 2013.

S!

Fragment-based drug design has emerged as an important methodology for lead discovery and drug design. Different with other studies focused on fragment library design and active fragment identification, a fragment-based strategy was developed in combination with 3D-QSAR for structural optimization in this study. Based on a validated scaffold or fragment hit, a series of structural optimization was conducted to convert it to lead compounds, including 3D-QSAR modelling, active site analysis, fragment-based structural optimization and evaluation of new molecules.

Zeolites

Mechanistic investigation of methanol to propene conversion catalyzed by H-beta zeolite: a two-layer ONIOM study

Yingxin Sun, Sheng Han[Shanghai Institute of Technology]

J. Mol.Mod., **19,** 5407-5422, 2013.

Two-layer ONIOM calculations have been carried out to study methanol to propene (MTP) conversion reactions catalyzed by H-beta zeolite. On the basis of the so-called side-chain hydrocarbon pool (HCP) mechanism, this work proposes the complete catalytic cycle pathway for the MTP reaction. The cycle starts from the methylation of pentamethylbenzene (PMB), which leads to the formation of hexamethylbenzenium ion ($hexaMB^+$). Subsequent steps involving deprotonation, methylation, an internal H-shift, and a unimolecular CH_3-shift are required to produce propene and ethene.

Carbon Nanoparticles

Competitive Crystallization of a Propylene/Ethylene Random Copolymer Filled with a β-Nucleating Agent and Multi-Walled Carbon Nanotubes. Conventional and Ultrafast DSC Study

Dimitrios G. Papageorgiou, George Z. Papageorgiou, Evgeny Zhuravlev, Dimitrios Bikiaris, Christoph Schick, and Konstantinos Chrissafis [Aristotle University of Thessaloniki]

J. Phys. Chem. B., **117**, 14875–14884, 2013**.**

A propylene/ethylene polymeric matrix was reinforced by the simultaneous addition of a β-nucleating agent (calcium pimelate) and multi-walled carbon nanotubes (MWCNTs) in various concentrations. The present manuscript explores the competitive crystallization tendency that is caused by the presence of the two fillers. On the one hand, calcium pimelate forces the material to crystallize predominantly in the β-crystalline form, while, on the other, the strong α-nucleating ability of MWCNTs compels the material to develop higher α-crystalline content. An in-depth study has been performed on the nanocomposite samples by means of conventional, temperature-modulated, and differential fast scanning calorimetry (DFSC) under various dynamic and isothermal conditions.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

RNA-Pareto: interactive analysis of Pareto-optimal RNA sequence-structure alignments

Thomas Schnattinger ,Uwe Schöning ,Anita Marchfelder ,Hans A. Kestler [Ulm University]

Bioinformatics. **29**, 3102-3104, 2013.

Incorporating secondary structure information into the alignment process improves the quality of RNA sequence alignments. Instead of using fixed weighting parameters, sequence and structure components can be treated as different objectives and optimized simultaneously. The result is not a single, but a Pareto-set of equally optimal solutions, which all represent different possible weighting parameters. We now provide the interactive graphical software tool RNA-Pareto, which allows a direct inspection of all feasible results to the pairwise RNA sequence-structure alignment problem and greatly facilitates the exploration of the optimal solution set.

Bioinformatics and Cheminformatics (Cont'd)

DockAFM: benchmarking protein structures by docking under AFM topographs

Rui C. Chaves[CEA, iBEB, Service de Biochimie et Toxicologie Nucléaire] ,Jean-Luc Pellequer

Bioinformatics. **29**, 3230-3231, 2013.

Proteins can adopt a variety of conformations. We present a simple server for scoring the agreement between 3D atomic structures and experimental envelopes obtained by atomic force microscopy. Three different structures of immunoglobulins (IgG) or blood coagulation factor V activated were tested and their agreement with several topographical surfaces was computed. This approach can be used to test structural variability within a family of proteins.

Bioinformatic analysis of protein families for identification of variable amino acid residues responsible for functional diversity

Dmitry Suplatov, Daria Shalaeva, Evgeny Kirilin, Vladimir Arzhanik & Vytas Švedas[Lomonosov Moscow State University]

J. Biomol. Stru. and Dyn., 31, 75-87,*2013.*

Proteins within a single family usually share a common function but differ in more specific features and can be divided into subfamilies with different properties. Availability of genomic, structural, and functional information implemented into numerous databases provides new opportunities for bioinformatic analysis of homologous proteins. In this work, new method of bioinformatic analysis has been developed to identify subfamily-specific positions (SSPs) – conserved only within protein subfamilies, but different between subfamilies – that seem to play important role in functional diversity.

FAst MEtabolizer (FAME): A Rapid and Accurate Predictor of Sites of Metabolism in Multiple Species by Endogenous Enzymes

Johannes Kirchmair, Mark J. Williamson, Avid M. Afzal, Jonathan D. Tyzack, Alison P. K. Choy, Andrew Howlett, Patrik Rydberg, and Robert C. Glen [University of Cambridge]

J.Chem. Infor. and Mod. **53**, 2896–2907, 2013.

FAst MEtabolizer (FAME) is a fast and accurate predictor of sites of metabolism (SoMs). It is based on a collection of random forest models trained on diverse chemical data sets of more than 20 000 molecules annotated with their experimentally determined SoMs. Using a comprehensive set of available data, FAME aims to assess metabolic processes from a holistic point of view. It is not limited to a specific enzyme family or species. Besides a global model, dedicated models are available for human, rat, and dog metabolism; specific prediction of phase I and II metabolism is also supported.

APL@Voro: A Voronoi-Based Membrane Analysis Tool for GROMACS Trajectories

Gunther Lukat[University of Bielefeld], Jens Krüger, and Björn Sommer

J.Chem. Infor. and Mod. **53**, 2908–2925, 2013.

APL@Voro is a new program developed to aid in the analysis of GROMACS trajectories of lipid bilayer simulations. It can read a GROMACS trajectory file, a PDB coordinate file, and a GROMACS index file to create a two-dimensional geometric representation of a bilayer. Voronoi diagrams and Delaunay triangulations—generated for different selection models of lipids—support the analysis of the bilayer. The values calculated on the geometric structures can be visualized in a user-friendly interactive environment and, then, plotted and exported to different file types.

Bioinformatics and Cheminformatics (Cont'd)

MetalS^2: A Tool for the Structural Alignment of Minimal Functional Sites in Metal-Binding Proteins and Nucleic Acids

Claudia Andreini[University of Florence], Gabriele Cavallaro, Antonio Rosato, and Yana Valasatava

J.Chem. Infor. and Mod. **53**, 3064–3075, 2013.

We developed a new software tool, MetalS^2, for the structural alignment of Minimal Functional Sites (MFSs) in metal-binding biological macromolecules. MFSs are 3D templates that describe the local environment around the metal(s) independently of the larger context of the macromolecular structure. Such local environment has a determinant role in tuning the chemical reactivity of the metal, ultimately contributing to the functional properties of the whole system. On our example data sets, MetalS^2 unveiled structural similarities that other programs for protein structure comparison do not consistently point out and overall identified a larger number of structurally similar MFSs.

Protein Secondary Structure

Elucidating protein secondary structure with circular dichroism and a neural network

Vincent Hall, Anthony Nash, Evor Hines, Alison Rodger[University of Warwick]

J. Comp. Chem., **34**, 2774–2786, 2013.

Circular dichroism spectroscopy is a quick method for determining the average secondary structures of proteins, probing their interactions with their environment, and aiding drug discovery. This article describes the development of a self-organising map structure-fitting methodology named secondary structure neural network (SSNN) to aid this process and reduce the level of expertise required. SSNN uses a database of spectra from proteins with known X-ray structures; prediction of structures for new proteins is then possible.

Comparative or Homology Modeling

Building KCNQ1/KCNE1 Channel Models and Probing their Interactions by Molecular-Dynamics Simulations

Yu Xu, Yuhong Wang, Xuan-Yu Meng, Mei Zhang, Min Jiang, Meng Cui, Gea-Ny Tseng [Virginia Commonwealth University]

Biophysical Journal. **105**, 2461-2473, 2013.

A!

Design of I_{Ks}-targeting anti-arrhythmic drugs requires detailed three-dimensional structures of the KCNQ1/KCNE1 complex, a task made possible by Kv channel crystal structures (templates for KCNQ1 homology-modeling) and KCNE1 NMR structures. Our goal was to build KCNQ1/KCNE1 models and extract mechanistic information about their interactions by molecular-dynamics simulations in an explicit lipid/solvent environment. We validated our models by confirming two sets of model-generated predictions that were independent from the spatial restraints used in model-building.

Comparative or Homology Modeling (Cont'd)

Structure of Patt1 human proapoptotic histone acetyltransferase

Roch Paweł Jędrzejewski[University of Gdańsk and Medical University of Gdańsk], Rajmund Kaźmierkiewicz

J. Mol.Mod., **19,** 5533-5538, 2013.

The results of modeling of a novel human histone acetyltransferase Patt1 are presented here. This protein belongs to the GNAT GCN5 family and shows proapoptotic activity in human hepatocellular carcinoma cells. Patt1 is an attractive therapeutic target. The sequence analysis, fold recognition predictions and homology modeling of Patt1 protein structure were performed. N- and C- termini of Patt1 were unstructured. Central part revealed classical GNAT fold–central 7-stranded beta sheet core surrounded by intervening 4 alpha helices.

Protein Confirmational Analysis

Refinement of the application of the GROMOS 54A7 force field to β-peptides

Zhixiong Lin, Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

J. Comp. Chem., **34**, 2796–2805, 2013.

In this study, a hexa-β-peptide whose conformational equilibrium encompasses two different helical folds, a right-handed $2.7_{10/12}$-helix and a left-handed 3_{14}-helix, is simulated using different GROMOS force-field parameter sets. When applying the recently developed GROMOS 54A7 force field, a significant destabilization effect on the $2.7_{10/12}$-helix of the peptide is observed, and the agreement with the experimental NOE distance bounds is much worse compared with the ones using previous versions of the GROMOS force field.

Adaptive lambda square dynamics simulation: An efficient conformational sampling method for biomolecules

Jinzen Ikebe, Shun Sakuraba, Hidetoshi Kono [Japan Atomic Energy Agency]

J. Comp. Chem., **35**, 39–50, 2014.

A novel, efficient sampling method for biomolecules is proposed. The partial multicanonical molecular dynamics (McMD) was recently developed as a method that improved generalized ensemble (GE) methods to focus sampling only on a part of a system (GEPS); however, it was not tested well. We found that partial McMD did not work well for polylysine decapeptide and gave significantly worse sampling efficiency than a conventional GE. Herein, we elucidate the fundamental reason for this and propose a novel GEPS, adaptive lambda square dynamics (ALSD),

Efficient prediction of protein conformational pathways based on the hybrid elastic network model

Sangjae Seo, Yunho Jang, Pengfei Qian, Wing Kam Liu, Jae-Boong Choi, Byeong Soo Lim, Moon Ki Kim [Sungkyunkwan University]

J. Mol.Graph. and Mod., **47,** 25-36, 2014.

Various computational models have gained immense attention by analyzing the dynamic characteristics of proteins. Nonetheless, each method possesses limitations, mostly in computational outlay and physical reality. These limitations remind us that a new model or paradigm should advance theoretical principles to elucidate more precisely the biological functions of a protein and should increase computational efficiency. With these critical caveats, we have developed a new computational tool that satisfies both physical reality and computational efficiency.

Protein Confirmational Analysis (Cont'd)

Highlighting a π–π interaction: a protein modeling and molecular dynamics simulation study on *Anopheles gambiae*glutathione S-transferase 1-2

Yan Wang, Qing-Chuan Zheng, Ji-Long Zhang, Ying-Lu Cui, Qiao Xue, Hong-Xing Zhang[Jilin University]

J. Mol.Mod., **19,** 5213-5223, 2013.

Cytosolic insect theta class glutathione S-transferases (GSTs) have not been studied completely and their physiological roles are unknown. A detailed understanding of *Anopheles gambiae* GST (Aggst1-2) requires an accurate structure, which has not yet been determined. A high quality modelstructure of Aggst1-2 was constructed using homology modeling and the ligand–protein complexwas obtained by the docking method. Molecular dynamics (MD) simulations were carried out to study conformational changes and to calculate binding free energy.

Structural analysis and molecular dynamics simulations of novel δ-endotoxin*Cry*1Id from *Bacillus thuringiensis* to pave the way for development of novel fusion proteins against insect pests of crops

Budheswar Dehury, Mousumi Sahu, Jagajjit Sahu, Kishore Sarma, Priyabrata Sen, Mahendra K. Modi, Madhumita Barooah [Assam Agricultural University], Manabendra Dutta Choudhury

J. Mol.Mod., **19,** 5301-5216, 2013.

The theoretical three-dimensional structure of a novel δ-endotoxin Cry1Id (81 kDa) belonging to Cry1I class, toxic to many of the lepidopteran pests has been investigated through comparative modeling.Molecular dynamics (MD) simulations was carried out to characterize its structural and dynamical features at 10 ns in explicit solvent using the GROMACS version 4.5.4. Finally the simulated model was validated by the SAVES, WHAT IF, MetaMQAP, ProQ, ModFOLD and MolProbity servers. Despite low sequence identity with its structural homologs, Cry1Id not only resembles the previously reported Cry structures but also shares the common five conserved blocks of amino acid residues.

Collecting and Assessing Human Lactate Dehydrogenase-A Conformations for Structure-Based Virtual Screening

Rosa Buonfiglio, Mariarosaria Ferraro, Federico Falchi, Andrea Cavalli, Matteo Masetti[Alma Mater Studiorum−Università di Bologna], and Maurizio Recanatini

J.Chem. Infor. and Mod. **53**, 2792-2797, 2013.

Human lactate dehydrogenase-A (LDHA) is emerging as a promising anticancer target. Up to now, structure-based investigations for identifying inhibitors of this enzyme have not explicitly accounted for active site flexibility. In the present study, by combining replica exchange molecular dynamics with network and cluster analyses, we identified reliable LDHA conformations for structure-based ligand design. The selected conformations were challenged and validated by retrospective virtual screening simulations.

The Impact of Molecular Dynamics Sampling on the Performance of Virtual Screening against GPCRs

Ákos Tarcsay, Gábor Paragi, Márton Vass, Balázs Jójárt, Ferenc Bogár, and György M. Keserű [University of Szeged]

J.Chem. Infor. and Mod. **53**, 2990–2999, 2013.

S!

The formation of ligand–protein complexes requires simultaneous adaptation of the binding partners. In structure based virtual screening, high throughput docking approaches typically consider the ligand flexibility, but the conformational freedom of the protein is usually taken into account in a limited way. The goal of this study is to elaborate a methodology for incorporating protein flexibility to improve the virtual screening enrichments on GPCRs.

Protein Confirmational Analysis (Cont'd)

Molecular Dynamics Simulations of the Protonated G4 PAMAM Dendrimer in an Ionic Liquid System

Juan J. Freire[Universidad Nacional de Educación a Distancia (UNED)], Amirhossein Ahmadi, and Carl McBride

J. Phys. Chem. B., **117**, 15157–15164, 2013**.**

Molecular dynamics simulations have been carried out for the ionic liquid system constituted by totally protonated PAMAM-EDA cations and $Tf2N^-$ anions. The conformational characteristics of the PMAM dendrimer (particularly the density profile around the dendrimer center) are compared with those obtained for the same dendrimer in water. We also investigate other features, such as the location of anions relative to the dendrimer molecules, and the interpenetration of the dendrimer cations in the ionic liquid system.

A computational analysis of binding modes and conformation changes of MDM2 induced by p53 and inhibitor bindings

Jianzhong Chen[Shandong Jiaotong University], Jinan Wang, Weiliang Zhu, Guohui Li

J. Comp. Aided. Mol. Design, **27**, 965-974, 2013.

The cleft tends to become wider and more stable as MDM2 binds to the three binding partners, while unbound MDM2 shows a narrower and pretty flexible cleft, which agrees with recent experimental data and theoretical studies. It was also found that the binding of P4 and p53 stabilizes the motion of the loop L2 linking the helix α2 and β strand (β3), but the presence of MI63a makes the motion of L2 disordered. In addition, the binding free energies of the three partners to MDM2 were calculated using molecular mechanics generalized Born surface area to explain the binding modes of these three partners to MDM2.

Protein Structure Analysis

Beyond Terrestrial Biology: Charting the Chemical Universe of α-Amino Acid Structures

Markus Meringer, H. James Cleaves[Tokyo Institute of Technology], II, and Stephen J. Freeland

J.Chem. Infor. and Mod. **53**, 2851–2862, 2013.

α-Amino acids are fundamental to biochemistry as the monomeric building blocks with which cells construct proteins according to genetic instructions. However, the 20 amino acids of the standard genetic code represent a tiny fraction of the number of α-amino acid chemical structures that could plausibly play such a role, both from the perspective of natural processes by which life emerged and evolved, and from the perspective of human-engineered genetically coded proteins. Here, we use computer software based on graph theory and constructive combinatorics in order to conduct an efficient and exhaustive search of the chemical structures.

Experimentally Guided Structural Modeling and Dynamics Analysis of Hsp90–p53 Interactions: Allosteric Regulation of the Hsp90 Chaperone by a Client Protein

Kristin Blacklock and Gennady M. Verkhivker [Chapman University]

J.Chem. Infor. and Mod. **53**, 2962–2978, 2013.

A fundamental role of the Hsp90 chaperone system in mediating maturation of protein clients is essential for the integrity of signaling pathways involved in cell cycle control and organism development. Molecular characterization of Hsp90 interactions with client proteins is fundamental to understanding the activity of many tumor-inducing signaling proteins and presents an active area of structural and biochemical studies. In this work, we have probed mechanistic aspects of allosteric regulation of Hsp90 by client proteins via a detailed computational study of Hsp90 interactions with the tumor suppressor protein p53.

Protein Dynamics

A density functional theory study on peptide bond cleavage at aspartic residues: direct vs cyclic intermediate hydrolysis

Wichien Sang-aroon[Rajamangala University of Technology Isan], Vittaya Amornkitbamrung, Vithaya Ruangpornvisuti

J. Mol.Mod., **19,** 5501-5513, 2013.

In this work, peptide bond cleavages at carboxy- and amino-sides of the aspartic residue in a peptide model via direct (concerted and step-wise) and cyclic intermediate hydrolysis reaction pathways were explored computationally. The energetics, thermodynamic properties, rate constants, and equilibrium constants of all hydrolysis reactions, as well as their energy profiles were computed at the B3LYP/6-311++G(d,p) level of theory. The result indicated that peptide bond cleavage of the Asp residue occurred most preferentially via the cyclic intermediate hydrolysis pathway.

QSSPN: dynamic simulation of molecular interaction networks describing gene regulation, signalling and whole-cell metabolism in human cells

Ciarán P. Fisher, Nicholas J. Plant, J. Bernadette Moore, Andrzej M. Kierzek[University of Surrey]

Bioinformatics. **29**, 3181-3190, 2013.

Dynamic simulation of genome-scale molecular interaction networks will enable the mechanistic prediction of genotype–phenotype relationships. Despite advances in quantitative biology, full parameterization of whole-cell models is not yet possible. Simulation methods capable of using available qualitative data are required to develop dynamic whole-cell models through an iterative process of modelling and experimental validation.We formulate quasi-steady state Petri nets (QSSPN), a novel method integrating Petri nets and constraint-based analysis to predict the feasibility of qualitative dynamic behaviours in qualitative models of gene regulation, signalling and whole-cell metabolism.

Structural Effects of pH and Deacylation on Surfactant Protein C in an Organic Solvent Mixture: A Constant-pH MD Study

Catarina A. Carvalheda, Sara R. R. Campos, Miguel Machuqueiro, and António M. Baptista [Universidade Nova de Lisboa]

J.Chem. Infor. and Mod. **53**, 2979–2989, 2013.

The present constant-pH MD study of the acylated and deacylated isoforms of SP-C in a chloroform/methanol/water mixture, often used to mimic the membrane environment, shows that the loss of the acyl groups has a structural destabilizing effect and that the increase of pH promotes intraprotein contacts which contribute to the loss of helical structure in solution. These contacts result from the poor solvation of charged groups by the solvent mixture, which exhibits a limited membrane-mimetic character. Although a single SP-C molecule was used in the simulations, we propose that analogous intermolecular interactions may play a role in the early stages of the protein misfolding and aggregation in this mixture.

Internal Water and Microsecond Dynamics in Myoglobin

Shuji Kaieda [Lund University] and Bertil Halle

J. Phys. Chem. B., **117**, 14676–14687, 2013**.**

Myoglobin (Mb) binds diatomic ligands, like O_2, CO, and NO, in a cavity that is only transiently accessible. Crystallography and molecular simulations show that the ligands can migrate through an extensive network of transiently connected cavities but disagree on the locations and occupancy of internal hydration sites. We use water ^{2}H and ^{17}O magnetic relaxation dispersion to characterize the internal water molecules in Mb under physiological conditions. Equine carbonmonoxy Mb contains 4.5 ± 1.0 ordered internal water molecules with a mean survival time of 5.6 ± 0.5 μs at 25 °C.

Protein Dynamics (Cont'd)

Conformation and Dynamics at a Flexible Glycosidic Linkage Revealed by NMR Spectroscopy and Molecular Dynamics Simulations: Analysis of β-l-Fuc*p*-(1→6)-α-d-Glc*p*-OMe in Water Solution

Robert Pendrill, Elin Säwén, and Göran Widmalm [Stockholm University]

J. Phys. Chem. B., **117**, 14709–14722, 2013**.**

The intrinsic flexibility of carbohydrates facilitates different 3D structures in response to altered environments. At glycosidic (1→6)-linkages, three torsion angles are variable, and herein the conformation and dynamics of β-L-Fuc*p*-(1→6)-α-D-Glc*p*-OMe are investigated using a combination of NMR spectroscopy and molecular dynamics (MD) simulations. The disaccharide shows evidence of conformational averaging for the ψ and ω torsion angles, best explained by a four-state conformational distribution. Notably, there is a significant population of conformations having ψ = 85° (*clinal*) in addition to those having ψ = 180° (*antiperiplanar*). Moderate differences in ^{13}C R_1 relaxation rates are found to be best explained by axially symmetric tumbling in combination with minor differences in librational motion for the two residues,.

Extending RosettaDock with water, sugar, and pH for prediction of complex structures and affinities for CAPRI rounds 20–27

Krishna Praneeth Kilambi, Michael S. Pacella, Jianqing Xu, Jason W. Labonte, Justin R. Porter, Pravin Muthu, Kevin Drew, Daisuke Kuroda, Ora Schueler-Furman, Richard Bonneau and Jeffrey J. Gray[Johns Hopkins University]

Proteins: Stru. Fun. & Bioinf., **81**, 2201–2209, 2013.

In this study, RosettaDock and other novel Rosetta protocols were used to successfully predict four of the 10 blind targets. For example, for DNase domain of Colicin E2–Im2 immunity protein, RosettaDock and RosettaLigand were used to predict the positions of water molecules at the interface, recovering 46% of the native water-mediated contacts. For α-repeat Rep4–Rep2 and g-type lysozyme–PliG inhibitor complexes, homology models were built and standard and pH-sensitive docking algorithms were used to generate structures with interface RMSD values of 3.3 Å and 2.0 Å, respectively.

A!

Epitope Fluctuations in the Human Papillomavirus Are Under Dynamic Allosteric Control: A Computational Evaluation of a New Vaccine Design Strategy

Abhishek Singharoy, Abhigna Polavarapu, Harshad Joshi, Mu-Hyun Baik, and Peter Ortoleva[Indiana University]

J. Am. Chem. Soc., 2013, **135**, 18458–18468

The dynamic properties of the capsid of the human papillomavirus (HPV) type 16 were examined using classical molecular dynamics simulations. By systematically comparing the structural fluctuations of the capsid protein, a strong dynamic allosteric connection between the epitope containing loops and the h4 helix located more than 50 Å away is identified, which was not recognized thus far. Computer simulations show that restricting the structural fluctuations of the h4 helix is key to rigidifying the epitopes, which is thought to be required for eliciting a proper immune response.

Protein Dynamics (Cont'd)

Evaluation of Protein Elastic Network Models Based on an Analysis of Collective Motions

Edvin Fuglebakk, Nathalie Reuter, and Konrad Hinsen [Centre National de la Recherche Scientifique]

J. Chem. Theor. and Comp, **9**, 5618–5628, 2013.

Elastic network models (ENMs) are valuable tools for investigating collective motions of proteins, and a rich variety of simple models have been proposed over the past decade. A good representation of the collective motions requires a good approximation of the covariances between the fluctuations of the individual atoms. Nevertheless, most studies have validated such models only by the magnitudes of the single-atom fluctuations they predict. In the present study, we have quantified the agreement between the covariance structure predicted by molecular dynamics (MD) simulations and those predicted by a representative selection of proposed coarse-grained ENMs.

Free Energy Perturbation

Small molecule-mediated control of hydroxyapatite growth: Free energy calculations benchmarked to density functional theory

Zhijun Xu, Yang Yang, Ziqiu Wang,Donald Mkhonto, Cheng Shang, Zhi-Pan Liu, Qiang Cui, Nita Sahai[University of Akron]

J. Comp. Chem., **35**, 70–81, 2014.

The unique, plate-like morphology of hydroxyapatite (HAP) nanocrystals in bone lends to the hierarchical structure and functions of bone. Proteins enriched in phosphoserine (Ser-OPO_3) and glutamic acid (Glu) residues have been proposed to regulate crystal morphology; however, the atomic-level mechanisms remain unclear. Here, we use the umbrella sampling/weighted histogram analysis method to obtain the adsorption free energy of Ser-OPO_3 and Glu on HAP (100) and (001) surfaces to understand organic-mediated crystal growth. The calculated organic-water–mineral interfacial energies are carefully benchmarked to density functional theory calculations, with explicit inclusion of solvating water molecules around the adsorbate plus the Poisson–Boltzmann continuum model for long-range solvation effects.

High-Resolution Free-Energy Landscape Analysis of α-Helical Protein Folding: HP35 and Its Double Mutant

Polina V. Banushkina and Sergei V. Krivov [University of Leeds]

J. Chem. Theor. and Comp, **9**, 5257–5266, 2013.

The free-energy landscape can provide a quantitative description of folding dynamics, if determined as a function of an optimally chosen reaction coordinate. Here, we construct the optimal coordinate and the associated free-energy profile for all-helical proteins HP35 and its norleucine (Nle/Nle) double mutant, based on realistic equilibrium folding simulations [Piana et al. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 17845]. Our analysis gives detailed information about folding of the proteins and can serve as a rigorous common language for extensive comparison between experiment and simulation.

Ligand Binding/Docking

Insight into the molecular mechanism about lowered dihydrofolate binding affinity to dihydrofolate reductase-like 1 (DHFRL1)

Jian Gao, Wei Cui, Yuguo Du, Mingjuan Ji [University of Chinese Academy of Sciences]

J. Mol.Mod., **19,** 5187-5198, 2013.

Human dihydrofolate reductase-like 1 (DHFRL1) has been identified as a second human dihydrofolate reductase (DHFR) enzyme. Although DHFRL1 have high sequence homology with human DHFR, dihydrofolate (DHF) exhibits a lowered binding affinity to DHFRL1 and the corresponding molecular mechanism is still unknown. To address this question, we studied the binding of DHF to DHFRL1 and DHFR by using molecular dynamics simulation. Moreover, to investigate the role the 24th residue of DHFR/DHFRL1 plays in DHF binding, R24W DHFRL1 mutant was also studied.

Molecular docking of thiamine reveals similarity in binding properties between the prion protein and other thiamine-binding proteins

Nataraj S. Pagadala[University of Alberta], Trent C. Bjorndahl, Nikolay Blinov, Andriy Kovalenko, David S. Wishart

J. Mol.Mod., **19,** 5225-5235, 2013.

Prion-induced diseases are a global health concern. The lack of effective therapy and 100 % mortality rates for such diseases have made the prion protein an important target for drug discovery. Previous NMR experimental work revealed that thiamine and its derivatives bind the prion protein in a pocket near the N-terminal loop of helix 1, and conserved intermolecular interactions were noted between thiamine and other thiamine-binding proteins. To better understand the potential role of water in thiamine–prion binding, a docking study was employed using structural X-ray solvent.

Investigation of the binding network of IGF-I on the cavity surface of IGFBP4

Xin Chen[Henan University], Shuyan Zhu, Danhui Duan, Tao Wu, Qi Wang

J. Mol.Mod., **19,** 5257-5266, 2013.

Insulin-like growth factor-binding proteins (IGFBPs) control bioactivity and distribution of insulin-like growth factors (IGFs) through high-affinity complex of IGFBP and IGF. To get more insight into the binding interaction of IGF system, the site-directed mutagenesis and force-driving desorption methods were employed to study the interaction mechanism of IGFBP4 and IGF-I by molecular dynamics (MD) simulation. In IGF-I, residues Gly7 to Asp12 were found to be the hot spots and they mainly anchored on the N-domain of IGFBP4.

Molecular mechanism of HIV-1 gp120 mutations that reduce CD4 binding affinity

Kristin Kassler[Friedrich-Alexander-Universität Erlangen-Nürnberg] & Heinrich Sticht

J. Biomol. Stru. and Dyn., 31,52-64,*2013.*

The interaction of the HIV-1 fusion protein gp120 with its cellular receptor CD4 represents a crucial step of the viral infection process, thus rendering gp120 a promising target for the intervention with anti-HIV drugs. Naturally occurring mutations of gp120, however, can decrease its affinity for anti-infective ligands like therapeutic antibodies or soluble CD4. To understand this phenomenon on a structural level, we performed molecular dynamics simulations of two gp120 variants, which exhibit a significantly decreased binding of soluble CD4. In both variants, the exchange of a nonpolar residue byglutamate was identified as an important determinant for reduced binding.

Ligand Binding / Docking (Cont'd)

Insights into AT_1 Receptor Activation through AngII Binding Studies

Minos-Timotheos Matsoukas, Constantinos Potamitis, Panayiotis Plotas, Maria-Eleni Androutsou, George Agelis, John Matsoukas, and Panagiotis Zoumpoulakis [National Hellenic Research Foundation]

J.Chem. Infor. and Mod. **53**, 2798-2811, 2013.

A! & S!

This study investigates the binding of angiotensin II (AngII) to the angiotensin II type 1 receptor (AT_1R), taking into consideration several known activation elements that have been observed for G-protein-coupled receptors (GPCRs). In order to determine the crucial interactions of AngII upon binding, several MD simulations were implemented using AngII conformations derived from experimental data (NMR ROEs) and *in silico* flexible docking methodologies. An additional goal was to simulate the induced activation mechanism and examine the already known structural rearrangements of GPCRs upon activation.

Ligand Binding Determinants for Angiotensin II Type 1 Receptor from Computer Simulations

Minos-Timotheos Matsoukas, Arnau Cordomí, Santiago Ríos, Leonardo Pardo, and Theodore Tselios

J.Chem. Infor. and Mod. **53**, 2874–2883, 2013.

The ligand binding determinants for the angiotensin II type 1 receptor (AT_1R), a G protein-coupled receptor (GPCR), have been characterized by means of computer simulations. As a first step, a pharmacophore model of various known AT_1R ligands exhibiting a wide range of binding affinities was generated. Second, a structural model of AT_1R was built making use of the growing set of crystal structures of GPCRs, which was further used for the docking of the AT_1R ligands based on the devised pharmacophore model.

Investigating the hydrogen-bond acceptor site of the nicotinic pharmacophore model: a computational and experimental study using epibatidine-related molecular probes

Clelia Dallanoce, Giovanni Grazioso[Università degli Studi di Milano], Diego Yuri Pomè, Miriam Sciaccaluga, Carlo Matera, Cecilia Gotti, Sergio Fucile, Marco De Amici

J. Comp. Aided. Mol. Design, **27**, 975-987, 2013.

The binding mode of nicotinic agonists has been thoroughly investigated in the last decades. It is now accepted that the charged amino group is bound by a cation-π interaction to a conserved tryptophan residue, and that the aromatic moiety is projected into a hydrophobic pocket deeply located inside the binding cleft. In this study, we computationally analyzed the role of this water molecule as a putative hydrogen bond donor/acceptor moiety in the agonist binding site of the three most relevant heteromeric (α4β2, α3β4) and homomeric (α7) neuronal nicotinic acetylcholine receptor (nAChR) subtypes.

Enzyme Catalysis

How Does Catalase Release Nitric Oxide? A Computational Structure–Activity Relationship Study

Sai Lakshmana Vankayala, Jacqueline C. Hargis, and H. Lee Woodcock [University of South Florida]

J.Chem. Infor. and Mod. **53**, 2951-2961, 2013.

S!

Hydroxyurea (HU) is the only FDA approved medication for treating sickle cell disease in adults. The primary mechanism of action is pharmacological elevation of nitric oxide (NO) levels which induces propagation of fetal hemoglobin. HU is known to undergo redox reactions with heme based enzymes like hemoglobin and catalase to produce NO. However, specific details about the HU based NO release remain unknown. Experimental studies indicate that interaction of HU with human catalase compound I produces NO. Presently, we combine flexible receptor–flexible substrate induced fit docking (IFD) with energy decomposition analyses to examine the atomic level details of a possible key step in the clinical conversion of HU to NO.

Loop Interactions and Dynamics Tune the Enzymatic Activity of the Human Histone Deacetylase 8

Micha B. A. Kunze, David W. Wright, Nicolas D. Werbeck, John Kirkpatrick, Peter V. Coveney[Yale University], and D. Flemming Hansen

J. Am. Chem. Soc., 2013, **135**, 17862–17868

The human histone deacetylase 8 (HDAC8) is a key hydrolase in gene regulation and has been identified as a drug target for the treatment of several cancers. Previously the HDAC8 enzyme has been extensively studied using biochemical techniques, X-ray crystallography, and computational methods. Those investigations have yielded detailed information about the active site and have demonstrated that the substrate entrance surface is highly dynamic. Yet it has remained unclear how the dynamics of the entrance surface tune and influence the catalytic activity of HDAC8.

Structural functionality, catalytic mechanism modeling and molecular allergenicity of phenylcoumaran benzylic ether reductase, an olive pollen (Ole e 12) allergen

Jose C. Jimenez-Lopez[The University of Western Australia], Simeon O. Kotchoni, Maria C. Hernandez-Soriano, Emma W. Gachomo,Juan D. Alché

J. Comp. Aided. Mol. Design, **27**, 873-895, 2013.

S!

Isoflavone reductase-like proteins (IRLs) are enzymes with key roles in the metabolism of diverse flavonoids. Last identified olive pollen allergen (Ole e 12) is an IRL relevant for allergy amelioration, since it exhibits high prevalence among atopic patients. The goals of this study are the characterization of (A) the structural-functionality of Ole e 12 with a focus in its catalytic mechanism, and (B) its molecular allergenicity by extensive analysis using different molecular computer-aided approaches

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Protein-Protein Interactions

Flexible docking and refinement with a coarse-grained protein model using ATTRACT

Sjoerd de Vries and Martin Zacharias[Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **81**, 2167–2174, 2013.

A coarse-grained (CG) protein model implemented in the ATTRACT protein–protein docking program has been employed to predict protein–protein complex structures in CAPRI Rounds 22–27. For six targets, acceptable or better quality solutions have been submitted corresponding to ~60% of all targets. For one target, promising results on the prediction of the hydration structure at the protein–protein interface have been achieved. New approaches for the rapid flexible refinement have been developed based on a combination of atomistic representation of the bonded geometry and a CG description of nonbonded interactions.

Inclusion of the orientational entropic effect and low-resolution experimental information for protein–protein docking in Critical Assessment of PRedicted Interactions (CAPRI)

Sheng-You Huang, Chengfei Yan, Sam Z. Grinter, Shan Chang, Lin Jiang, Xiaoqin Zou[University of Missouri]

Proteins: Stru. Fun. & Bioinf., **81**, 2183–2191, 2013.

A!

Inclusion of entropy is important and challenging for protein–protein binding prediction. Here, we present a statistical mechanics-based approach to empirically consider the effect of orientational entropy. Specifically, we globally sample the possible binding orientations based on a simple shape-complementarity scoring function using an FFT-type docking method. Then, for each generated orientation, we calculate the probability through the partition function of the ensemble of accessible states, which are assumed to be represented by the set of nearby binding modes. For each mode, the interaction energy is calculated using our ITScorePP scoring function that was developed in our laboratory based on principles of statistical mechanics.

Expanding the frontiers of protein–protein modeling: From docking and scoring to binding affinity predictions and other challenges

Chiara Pallara, Brian Jiménez-García, Laura Pérez-Cano, Miguel Romero-Durana, Albert Solernou, Solène Grosdidier, Carles Pons, Iain H. Moal and Juan Fernandez-Recio

Proteins: Stru. Fun. & Bioinf., **81**, 2192–2200, 2013.

In addition to protein–protein docking, this CAPRI edition included new challenges, like protein–water and protein–sugar interactions, or the prediction of binding affinities and $\Delta\Delta G$ changes upon mutation. In this edition, available information on known interface residues hardly made any difference for our predictions. In one of the targets, the inclusion of available experimental small-angle X-ray scattering (SAXS) data using our *pyDockSAXS* approach slightly improved the predictions. In addition to the standard protein–protein docking assessment, new challenges were proposed.

Using the concept of transient complex for affinity predictions in CAPRI rounds 20–27 and beyond

Sanbo Qin and Huan-Xiang Zhou[Florida State University]

Proteins: Stru. Fun. & Bioinf., **81**, 2229–2236, 2013.

In developing a computational method for predicting protein–protein association rate constants, we introduced the concept of transient complex after mapping the interaction energy surface. The transient complex is located at the outer boundary of the bound-state energy well, having near-native separation and relative orientation between the subunits but not yet formed most of the short-range native interactions. We found that the width of the binding funnel and the electrostatic interaction energy of the transient complex are among the

features predictive of binders and binding affinities.

Protein-Protein Interactions (Cont'd)

Solvent Binding Analysis and Computational Alanine Scanning of the Bovine Chymosin–Bovine κ-Casein Complex Using Molecular Integral Equation Theory

David S. Palmer, Jesper Sørensen, Birgit Schiøtt, and Maxim V. Fedorov [University of Strathclyde]

J. Chem. Theor. and Comp, **9**, 5706–5717, 2013.

We demonstrate that the relative binding thermodynamics of single-point mutants of a model protein–peptide complex (the bovine chymosin–bovine κ-casein complex) can be calculated accurately and efficiently using molecular integral equation theory. The results are shown to be in good overall agreement with those obtained using implicit continuum solvation models. Unlike the implicit continuum models, however, molecular integral equation theory provides useful information about the distribution of solvent density.

Membrane Proteins and Lipid Peptide Interactions

Molecular dynamics approach to investigate the coupling of the hydrophilic–lipophilic balance with the configuration distribution function in biosurfactant-based emulsions

Melissa Álvarez Vanegas, Angie Macías Lozano, Vanessa Núñez Vélez, Nathalia Garcés Ferreira,Harold Castro Barrera, Oscar Álvarez Solano, Andrés Fernando González Barrios[Universidad de los Andes]

J. Mol.Mod., **19,** 5539-5543, 2013.

In the work reported here, molecular dynamics simulations were used to elucidate the mechanism of layer formation and micellar structure for different combinations of valine–aspartic acid peptides in dodecane–water emulsions, as well as their associations with the hydrophilic–lipophilic balance. The peptide–dodecane radial distribution function showed that the first peak intensity was inversely correlated with the hydrophilic–lipophilic balance; moreover, the oscillatory structural forces became increasingly prominent when the hydrophilic–lipophilic balance was decreased. Our results seem to indicate that the radial distribution function could be utilized to evaluate the stabilities of emulsions of peptides via molecular simulations.

Biomembrane simulations of 12 lipid types using the general amber force field in a tensionless ensemble

João T.S. Coimbra, Sérgio F. Sousa, Pedro A. Fernandes, Maria Rangel & Maria J. Ramos [Universidade do Porto]

*J. Biomol. Stru. and Dyn., 31,*88-103*,2013.*

The AMBER family of force fields is one of the most commonly used alternatives to describe proteins and drug-like molecules in molecular dynamics simulations. However, the absence of a specific set of parameters for lipids has been limiting the widespread application of this force field in biomembrane simulations, including membrane protein simulations and drug-membrane simulations. Here, we report the systematic parameterization of 12 common lipid types consistent with the General Amber Force Field (GAFF), with charge-parameters determined with RESP at the HF/6–31G(d) level of theory, to be consistent with AMBER.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Binding Affinity Prediction for Protein–Ligand Complexes Based on β Contacts and B Factor

Qian Liu, Chee Keong Kwoh, and Jinyan Li [University of Technology, Sydney]

J.Chem. Infor. and Mod. **53**, 3076–3085, 2013.

Accurate determination of protein–ligand binding affinity is a fundamental problem in biochemistry useful for many applications including drug design and protein–ligand docking. A number of scoring functions have been proposed for the prediction of protein–ligand binding affinity. However, accurate prediction is still a challenging problem because poor performance is often seen in the evaluation under the leave-one-cluster-out cross-validation (LCOCV). We introduce a new scoring function named B2BScore to improve the prediction performance. B2BScore integrates two physicochemical properties for protein–ligand binding affinity prediction.

Spontaneous Membrane-Translocating Peptide Adsorption at Silica Surfaces: A Molecular Dynamics Study

Karina Kubiak-Ossowska, Glenn Burley, Siddharth V. Patwardhan, and Paul A. Mulheran [University of Strathclyde]

J. Phys. Chem. B., **117**, 14666–14675, 2013**.**

Spontaneous membrane-translocating peptides (SMTPs) have recently been shown to directly penetrate cell membranes. Adsorption of a SMTP, and some engineered extensions, at model silica surfaces is studied herein using fully atomistic molecular dynamics simulations in order to assess their potential to construct novel drug delivery systems. The simulations are designed to reproduce the electric fields above single, siloxide-rich charged surfaces, and the trajectories indicate that the main driving force for adsorption is electrostatic.

A!

Detection of peptide-binding sites on protein surfaces: The first step toward the modeling and targeting of peptide-mediated interactions

Assaf Lavi, Chi Ho Ngan, Dana Movshovitz-Attias, Tanggis Bohnuud, Christine Yueh, Dmitri Beglov, Ora Schueler-Furman [The Hebrew University]and Dima Kozakov

Proteins: Stru. Fun. & Bioinf., **81**, 2096–2105, 2013.

Here, we present *PeptiMap*, a protocol for the accurate mapping of peptide binding sites on protein structures. Our method is based on experimental evidence that peptide-binding sites also bind small organic molecules of various shapes and polarity. Using an adaptation of *ab initio* ligand binding site prediction based on fragment mapping (FTmap), we optimize a protocol that specifically takes into account peptide binding site characteristics. In a high-quality curated set of peptide-protein complex structures *PeptiMap* identifies for most the accurate site of peptide binding among the top ranked predictions.

Passive Membrane Permeability: Beyond the Standard Solubility-Diffusion Model

Giulia Parisio[Università di Padova], Matteo Stocchero, and Alberta Ferrarini

J. Chem. Theor. and Comp, **9**, 5236–5246, 2013.

The spontaneous diffusion of solutes through lipid bilayers is still a challenge for theoretical predictions. Since permeation processes remain beyond the capabilities of unbiased molecular dynamics simulations, an alternative strategy is currently adopted to gain insight into their mechanism and time scale. Here, we discuss the limitations of the standard solubility-diffusion approach and propose a more general description of membrane translocation as a diffusion process on a free energy surface, which is a function of the translational and rotational degrees of freedom of the molecule.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Surface-Tension Replica-Exchange Molecular Dynamics Method for Enhanced Sampling of Biological Membrane Systems

Takaharu Mori, Jaewoon Jung, and Yuji Sugita [RIKEN Advanced Institute for Computational Science]

J. Chem. Theor. and Comp, **9**, 5629–5640 2013.

Conformational sampling is fundamentally important for simulating complex biomolecular systems. The generalized-ensemble algorithm, especially the temperature replica-exchange molecular dynamics method (T-REMD), is one of the most powerful methods to explore structures of biomolecules such as proteins, nucleic acids, carbohydrates, and also of lipid membranes. T-REMD simulations have focused on soluble proteins rather than membrane proteins or lipid bilayers, because explicit membranes do not keep their structural integrity at high temperature. Here, we propose a new generalized-ensemble algorithm for membrane systems.

The Movable Type Method Applied to Protein–Ligand Binding

Zheng Zheng, Melek N. Ucisik, and Kenneth M. Merz

J. Chem. Theor. and Comp, **9**, 5526–5538, 2013.

S!

Accurately computing the free energy for biological processes like protein folding or protein–ligand association remains a challenging problem. Both describing the complex intermolecular forces involved and sampling the requisite configuration space make understanding these processes innately difficult. Herein, we address the sampling problem using a novel methodology we term "movable type" (MT). Conceptually it can be understood by analogy with the evolution of printing and, hence, the name movable type.

Effects of Phospholipid Composition on the Transfer of a Small Cationic Peptide Across a Model Biological Membrane

Daniel Bonhenry, Mounir Tarek[Université de Lorraine], and François Dehez

J. Chem. Theor. and Comp, **9**, 5675–5684, 2013.

The transfer of a lysine amino acid analogue across phospholipid membrane models was investigated using molecular-dynamics simulations. The evolution of the protonation state of this small peptide as a function of its position inside the membrane was studied by determining the local pK_a by means of free-energy calculations. Permeability and mean-first-passage time were evaluated and showed that the transfer occurs on the submillisecond time scale. Comparative studies were conducted to evaluate changes in the pK_a arising from differences in the phospholipid chemical structure.

Computational analysis of local membrane properties

Vytautas Gapsys[Max Planck Institute for Biophysical Chemistry], Bert L. de Groot, Rodolfo Briones

J. Comp. Aided. Mol. Design, **27**, 845-858, 2013.

A number of proteins, including channels, transporters, receptors and short peptides are embedded in lipid bilayers and tightly interact with phospholipids. While the experimental measurements report on the spatial and/or temporal average membrane properties, simulation results are not restricted to the average properties. In the current study, we present a collection of methods for an efficient local membrane property calculation, comprising bilayer thickness, area per lipid, deuterium order parameters, Gaussian and mean curvature.

Protein-Nucleic acid Interactions

Insight into the interaction between DNA bases and defective graphenes: Covalent or non-covalent

Zhenfeng Xu, Biswa Ranjan Meher, Darnashley Eustache, Yixuan Wang [Albany State University]

J. Mol.Graph. and Mod., **47,** 8-17, 2014.

In the present study the adsorptions of the nucleobases, adenine (A), cytosine (C), guanine, (G), and thymine (T) on pristine and defective graphenes, are fully optimized using a hybrid-meta GGA density functional theory (DFT), M06-2X/6-31G*, and the adsorption energies are then refined with both M06-2X and B97-D/6-311++G**. Graphene is modeled as nano-clusters of $C_{72}H_{24}$, $C_{71}H_{24}$, and $C_{70}H_{24}$ for pristine, mono- and di-vacant defective graphenes, respectively, supplemented by a few larger ones.

Unveiling the Groove Binding Mechanism of a Biocompatible Naphthalimide-Based Organoselenocyanate with Calf Thymus DNA: An "Ex Vivo" Fluorescence Imaging Application Appended by Biophysical Experiments and Molecular Docking Simulations

Soumya Sundar Mati, Somnath Singha Roy, Sayantani Chall, Sudin Bhattacharya, and Subhash Chandra Bhattacharya [Jadavpur University]

J. Phys. Chem. B., **117**, 14655–14665, 2013**.**

The present study embodies a detailed investigation of the binding modes of a potential anticancer and neuroprotective fluorescent drug, 2-(5-selenocyanato-pentyl)-6-chloro benzo[de]isoquinoline-1,3-dione (NPOS) with calf thymus DNA (ctDNA). Experimental results based on spectroscopy, isothermal calorimetry, electrochemistry aided with DNA-melting, and circular dichroism studies unambiguously established the formation of a groove binding network between the NPOS and ctDNA. Molecular docking analysis ascertained a *hydrogen bonding mediated* 'A-T rich region of B-DNA' as the preferential docking site for NPOS.

Predicting protein–DNA interactions by full search computational docking

Victoria A. Roberts[University of California], Michael E. Pique, Lynn F. Ten Eyck and Sheng Li

Proteins: Stru. Fun. & Bioinf., **81**, 2106–2118, 2013.

Protein–DNA interactions are essential for many biological processes. X-ray crystallography can provide high-resolution structures, but protein-DNA complexes are difficult to crystallize and typically contain only small DNA fragments. Thus, there is a need for computational methods that can provide useful predictions to give insights into mechanisms and guide the design of new experiments. We used the program DOT, which performs an exhaustive, rigid-body search between two macromolecules, to investigate four diverse protein–DNA interactions. Here, we compare our computational results with subsequent experimental data on related systems.

Nucleic Acids

QM-MM simulations on p53-DNA complex: a study of hot spot and rescue mutants

Shruti Koulgi, Archana Achalere, Neeru Sharma, Uddhavesh Sonavane, Rajendra Joshi[Pune University Campus]

J. Mol.Mod., **19,** 5545-5559, 2013.

p53 is a transcription factor involved in the expression of a number of downstream genes in response to genotoxic stress. It is activated through post translation modifications in normal as well as cancerous cells. However, due to mutations occurring in p53 in cancer cells it is not able to perform its function of DNA binding which leads to cell proliferation. It is found to be mutated in 50 % of the cancers. These mutations occur at a high frequency in the DNA binding region of the p53. Among the known seven hot spot cancer mutations G245S, R249S, and R273C have been studied here using QM-MM simulations.

Elastic Network Models of Nucleic Acids Flexibility

Piotr Setny[University of Warsaw] and Martin Zacharias

J. Chem. Theor. and Comp, **9**, 5460–5470, 2013.

Elastic network models (ENMs) are a useful tool for describing large scale motions in protein systems. While they are well validated in the context of proteins, relatively little is known about their applicability to nucleic acids, whose different architecture does not necessarily warrant comparable performance. In this study we thoroughly evaluate and optimize the efficiency of popular ENMs for capturing RNA and DNA flexibility.

Surfaces, Catalysts, and Materials Subjects

Chemical mechanism of surface-enhanced raman scattering spectrum of pyridine adsorbed on Ag cluster: *Ab initio* molecular dynamics approach

Jen-Ping Su, Yung-Ting Lee, Shao-Yu Lu, Jyh Shing Lin [Tamkang University]

J. Comp. Chem., **34**, 2806–2815, 2013.

The surface-enhanced Raman scattering (SERS) spectrum of pyridine adsorbed on Ag_{20} cluster (pyridine-Ag_{20}) at room temperature is calculated by performing *ab initio* molecular dynamics simulations in connection with a Fourier transform of the polarizability autocorrelation function to investigate the static chemical enhancement behind the SERS spectrum. The five enhanced vibrational modes of pyridine, namely, υ_{6a}, υ_{1}, υ_{12}, υ_{9a}, and υ_{8a}, can be assigned and identified by using a new analytical scheme, namely, single-frequency-pass filter, which is based on a Fourier transform filtering technique.

Restructuring of a Model Hydrophobic Surface: Monte Carlo Simulations Using a Simple Coarse-Grained Model

Changsun Eun, Jhuma Das, and Max L. Berkowitz [University of North Carolina at Chapel Hill]

When immersed in water, an ionic mica plate initially covered by a monolayer of surfactants rearranges to a surface inhomogeneously covered by patches of surfactant bilayer and bare mica. The model considers four species that can cover lattice sites of a surface. These species include (i) a surfactant molecule with its headgroup down, (ii) surfactant molecule with the headgroup up, (iii) a surfactant dimer arranged in a tail-

J. Phys. Chem. B., **117**, 15584–15590, 2013**.**

to-tail configuration, which is a part of a bilayer, and (iv) a mica lattice site covered by water. We consider that only nearest neighbors on the lattice interact and describe the interactions by an interaction matrix.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Using Random Forest To Model the Domain Applicability of Another Random Forest Model

Robert P. Sheridan [Merck ResearchLaboratories]

J.Chem. Infor. and Mod. **53**, 2837–2850, 2013.

In QSAR, a statistical model is generated from a training set of molecules (represented bychemical descriptors) and their biological activities. We will call this traditional type of QSAR model an "activity model". The activity model can be used to predict the activities of molecules not in the training set. A relatively new subfield for QSAR is domain applicability. The aim is to estimate the reliability of prediction of a specific molecule on a specific activity model. A number of different metrics have been proposed in the literature for this purpose. It is desirable to build a quantitative model of reliability against one or more of these metrics.

Potentials and Parameters

Rapid parameterization of small molecules using the force field toolkit

Christopher G. Mayne ,Jan Saam,Klaus Schulten , Emad Tajkhorshid [University of Illinois at Urbana-Champaign],James C. Gumbart,

J. Comp. Chem., **34**, 2757–2770, 2013.

The inability to rapidly generate accurate and robust parameters for novel chemical matter continues to severely limit the application of molecular dynamics simulations to many biological systems of interest, especially in fields such as drug discovery. Although the release of generalized versions of common classical force fields, for example, General Amber Force Field and CHARMM General Force Field, have posited guidelines for parameterization of small molecules, many technical challenges remain that have hampered their wide-scale extension.

Data Driven, Predictive Molecular Dynamics for Nanoscale Flow Simulations under Uncertainty

Panagiotis Angelikopoulos, Costas Papadimitriou, and Petros Koumoutsakos [University of Thessaly]

J. Phys. Chem. B., **117**, 14808–14816, 2013**.**

In this work, we show that experimental and MD investigations can be consolidated through a rigorous uncertainty quantification framework. We employ a Bayesian probabilistic framework for large scale MD simulations of graphitic nanostructures in aqueous environments. We assess the uncertainties in the MD predictions for quantities of interest regarding wetting behavior and hydrophobicity. We focus on three representative systems: water wetting of graphene, the aggregation of fullerenes in aqueous solution, and the

water transport across carbon nanotubes.

Potentials and Parameters (Cont'd)

Development of an Effective Polarizable Bond Method for Biomolecular Simulation

Xudong Xiao, Tong Zhu, Chang G. Ji, and John Z. H. Zhang [East China Normal University]

J. Phys. Chem. B., **117**, 14885–14893, 2013**.**

An effective polarizable bond (EPB) model has been developed for computer simulation of proteins. In this partial polarizable approach, all polar groups of amino acids are treated as polarizable, and the relevant polarizable parameters were determined by fitting to quantum calculated electrostatic properties of these polar groups. Extensive numerical tests on a diverse set of proteins (including 1IEP, 1MWE, 1NLJ, 4COX, 1PGB, 1K4C, 1MHN, 1UBQ, 1IGD) showed that this EPB model is robust in MD simulation and can correctly describe the structure and dynamics of proteins (both soluble and membrane proteins).

Forcefield_PTM: *Ab Initio* Charge and AMBER Forcefield Parameters for Frequently Occurring Post-Translational Modifications

George A. Khoury, Jeff P. Thompson, James Smadbeck, Chris A. Kieslich, and Christodoulos A. Floudas [Princeton University]

J. Chem. Theor. and Comp, **9**, 5653–5674, 2013.

In this work, we introduce Forcefield_PTM, a set of AMBER forcefield parameters consistent with ff03 for 32 common post-translational modifications. Partial charges were calculated through *ab initio* calculations and a two-stage RESP-fitting procedure in an ether-like implicit solvent environment. The charges were found to be generally consistent with others previously reported for phosphorylated amino acids, and trimethyllysine, using different parametrization methods. Pairs of modified structures and their corresponding unmodified structures were curated from the PDB for both single and multiple modifications.

Estimation of Interaction Potentials through the Configurational Temperature Formalism

Martin Mechelke and Michael Habeck [University Göttingen]

J. Chem. Theor. and Comp, **9**, 5685–5692, 2013.

Molecular interaction potentials are difficult to measure experimentally and hard to compute from first principles, especially for large systems such as proteins. It is therefore desirable to estimate the potential energy that underlies a thermodynamic ensemble from simulated or experimentally determined configurations. This inverse problem of statistical mechanics is challenging because the various potential energy terms can exhibit subtle indirect and correlated effects on the resulting ensemble. A direct approach would try to adapt the force field parameters such that the given configurations are highly probable in the resulting ensemble.

Efficient Parameter Estimation of Generalizable Coarse-Grained Protein Force Fields Using Contrastive Divergence: A Maximum Likelihood Approach

Csilla Várnai, Nikolas S. Burkoff, and David L. Wild [University of Warwick]

J. Chem. Theor. and Comp, **9**, 5718–5733, 2013.

Maximum Likelihood (ML) optimization schemes are widely used for parameter inference. They maximize the likelihood of some experimentally observed data, with respect to the model parameters iteratively, following the gradient of the logarithm of the likelihood. Here, we employ a ML inference scheme to infer a generalizable, physics-based coarse-grained protein model (which includes Gō-like biasing terms to stabilize secondary structure elements in room-temperature simulations),

using native conformations of a training set of proteins as the observed data.

Solvation Energy

Incorporating the excluded solvent volume and surface charges for computing solvation free energy

Pei-Kun Yang [I-SHOU University]

J. Comp. Chem., **35**, 62–69, 2014.

Gauss's law or Poisson's equation is conventionally used to calculate solvation free energy. However, the near-solute dielectric polarization from Gauss's law or Poisson's equation differs from that obtained from molecular dynamics (MD) simulations. To mimic the near-solute dielectric polarization from MD simulations, the first-shell water was treated as two layers of surface charges, the densities of which are proportional to the electric field at the solvent molecule that is modeled as a hard sphere. The intermediate water was treated as a bulk solvent. An equation describing the solvation free energy of ions using this solvent scheme was derived using the TIP3P water model.

Variational Optimization of an All-Atom Implicit Solvent Force Field To Match Explicit Solvent Simulation Data

Sandro Bottaro, Kresten Lindorff-Larsen, and Robert B. Best [University of Cambridge]

J. Chem. Theor. and Comp, **9**, 5641–5652, 2013.

The development of accurate implicit solvation models with low computational cost is essential for addressing many large-scale biophysical problems. Here, we present an efficient solvation term based on a Gaussian solvent-exclusion model (EEF1) for simulations of proteins in aqueous environment, with the primary aim of having a good overlap with explicit solvent simulations, particularly for unfolded and disordered states – as would be needed for multiscale applications. In order to achieve this, we have used a recently proposed coarse-graining procedure based on minimization of an entropy-related objective function to train the model to reproduce the equilibrium distribution obtained from explicit water simulations.

Molecular Dynamics

Changes to the Structure and Dynamics in Mutations of $A\beta_{21–30}$ Caused by Ions in Solution

Micholas Dean Smith and Luis Cruz [Drexel University]

J. Phys. Chem. B., **117**, 14907–14915, 2013**.**

The structure and dynamics of the 21–30 fragment of the amyloid β-protein ($A\beta_{21–30}$) and its Dutch [Glu22Gln], Arctic [Glu22Gly], and Iowa [Asp23Asn] isoforms are of considerable importance, as their folding may play an important role in the pathogenesis of sporadic and familial forms of Alzheimer's disease and cerebral amyloid angiopathy. A full understanding of this pathologic folding in in vivo environments is still elusive. Here we examine the interactions and effects of two neurobiologically relevant salts ($CaCl_2$ and KCl) on the structure and dynamics of $A\beta_{21–30}$ decapeptide monomers containing the Dutch, Arctic, and Iowa charge-modifying point mutations using isobaric–isothermal (NPT) explicit water all-atom molecular-dynamics simulations.

Molecular Dynamics (Cont'd)

Exploring the Dynamic Behaviors and Transport Properties of Gas Molecules in a Transmembrane Cyclic Peptide Nanotube

Rui Li, Jianfen Fan[Soochow University], Hui Li, Xiliang Yan, and Yi Yu

J. Phys. Chem. B., **117**, 14916–14927, 2013**.**

The dynamic behaviors and transport properties of O_2, CO_2, and NH_3 molecules through a transmembrane cyclic peptide nanotube (CPNT) of 8×cyclo-$(WL)_4$/POPE have been investigated by steered molecular dynamics (SMD) simulations and adaptive biasing force (ABF) samplings. Different external forces are needed for three gas molecules to enter the channel. The periodic change of the pulling force curve for a gas traveling through the channel mainly arises from the regular and periodic arrangement of the composed CP subunits of the CPNT. Radial distribution functions (RDFs) between gas and water disclose the density decrease of channel water, which strongly aggravates the discontinuity of H-bond formation between a gas molecule and the neighboring water.

Molecular Dynamics Simulations Accelerated by GPU for Biological Macromolecules with a Non-Ewald Scheme for Electrostatic Interactions

Tadaaki Mashimo, Yoshifumi Fukunishi, Narutoshi Kamiya, Yu Takano, Ikuo Fukuda, and Haruki Nakamura [Osaka University]

J. Chem. Theor. and Comp, **9**, 5599–5609, 2013.

A molecular dynamics (MD) simulation program for biological macromolecules was implemented with a non-Ewald scheme for long-ranged electrostatic interactions and run on a general purpose graphics processing unit (GPU). We recently developed several non-Ewald methods to compute the electrostatic energies with high precision. In particular, the zero-dipole summation (ZD) method, which takes into account the neutralities of charges and dipoles in a truncated subset, enables the calculation of electrostatic interactions with high accuracy and low computational cost, and its algorithm is simple enough to be implemented in a GPU.

QM and QM/MM

QuanPol: A full spectrum and seamless QM/MM program

Nandun M. Thellamurege, Dejun Si, Fengchao Cui, Hongbo Zhu, Rui Lai, Hui Li [University of Nebraska-Lincoln]

J. Comp. Chem., **34**, 2816–2833, 2013.

The quantum chemistry polarizable force field program (QuanPol) is implemented to perform combined quantum mechanical and molecular mechanical (QM/MM) calculations with induced dipole polarizable force fields and induced surface charge continuum solvation models. The QM methods include Hartree–Fock method, density functional theory method (DFT), generalized valence bond theory method, multiconfiguration self-consistent field method, Møller–Plesset perturbation theory method, and time-dependent DFT method.

QM and QM/MM (Cont'd)

Can tautomerization of the A•T Watson–Crick base pair via double proton transfer provoke point mutations during DNA replication? A comprehensive QM and QTAIM analysis

Ol'ha O. Brovarets & Dmytro M. Hovorun [Taras Shevchenko National University of Kyiv]

J. Biomol. Stru. and Dyn., 31,(12) 1358-1369,*2013.*

Trying to answer the question posed in the title, we have carried out a detailed theoretical investigation of the biologically important mechanism of the tautomerization of the A•T Watson–Crick DNA base pair, information that is hard to establish experimentally. By combining theoretical investigations at the MP2 and density functional theory levels of QM theory with quantum theory of atoms in molecules analysis, the tautomerization of the A•T Watson–Crick base pair by the double proton transfer (DPT) was comprehensively studied in vacuo and in the continuum with a low dielectric constant ($\epsilon = 4$) corresponding to a hydrophobic interfaces ofprotein–nucleic acid interactions.

Reactivation steps by 2-PAM of tabun-inhibited human acetylcholinesterase: reducing the computational cost in hybrid QM/MM methods

Arlan da Silva Gonçalves[Federal Institute of Education Science and Technology (IFES)], Tanos Celmar Costa França, Melissa Soares Caetano & Teodorico Castro Ramalho

J. Biomol. Stru. and Dyn., 31, 301-307,*2013.*

The present work describes a simple integrated Quantum Mechanics/Molecular Mechanics method developed to study the reactivation steps by pralidoxime (2-PAM) of acetylcholinesterase (AChE) inhibited by the neurotoxic agent Tabun. The method was tested on an AChE model and showed to be able to corroborate most of the results obtained before, through a more complex and time-consuming methodology, proving to be suitable to this kind of mechanistic study at a lower computational cost.

Quantum Mechanics/Molecular Mechanics Restrained Electrostatic Potential Fitting

Steven K. Burger[University of Toronto], Jeremy Schofield, and Paul W. Ayers

J. Phys. Chem. B., **117**, 14960–14966, 2013**.**

We present a QM/MM method to evaluate the partial charges of amino acid residues for use in MM potentials based on their protein environment. For each residue of interest, the nearby residues are included in the QM system while the rest of the protein is treated at the MM level of theory. After a short structural optimization, the partial charges of the central residue are fit to the electrostatic potential using the restrained electrostatic potential (RESP) method. The resulting charges and electrostatic potential account for the individual environment of the residue, although they lack the transferable nature of library partial charges.

Quantum Mechanics-Based Scoring Rationalizes the Irreversible Inactivation of Parasitic *Schistosoma mansoni* Cysteine Peptidase by Vinyl Sulfone Inhibitors

Jindřich Fanfrlík, Pathik S Brahmkshatriya, Jan Řezáč, Adéla Jílková, Martin Horn, Michael Mareš, Pavel Hobza, and Martin Lepšík [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **117**, 14973–14982, 2013**.**

The quantum mechanics (QM)-based scoring function that we previously developed for the description of noncovalent binding in protein–ligand complexes has been modified and extended to treat covalent binding of inhibitory ligands. The enhancements are (i) the description of the covalent bond breakage and formation using hybrid QM/semiempirical QM (QM/SQM) restrained optimizations and (ii) the addition of the new $\Delta G_{cov}'$ term to the noncovalent score, describing the "free" energy difference between the covalent and noncovalent complexes. This enhanced QM-based scoring function is applied to a series of 20 vinyl sulfone-

based inhibitory compounds inactivating the cysteine peptidase cathepsin B1 of the *Schistosoma mansoni* parasite (SmCB1).

QM and QM/MM (Cont'd)

Quantum Trajectory-Electronic Structure Approach for Exploring Nuclear Effects in the Dynamics of Nanomaterials

Sophya Garashchuk[University of South Carolina], Jacek Jakowski, Lei Wang, and Bobby G. Sumpter

J. Chem. Theor. and Comp, **9**, 5221–5235, 2013.

A massively parallel, direct quantum molecular dynamics method is described. The method combines a quantum trajectory (QT) representation of the nuclear wave function discretized into an ensemble of trajectories with an electronic structure (ES) description of electrons, namely using the density functional tight binding (DFTB) theory. Quantum nuclear effects are included into the dynamics of the nuclei via quantum corrections to the classical forces. A massively parallel implementation, based on the message passing interface allows for efficient simulations of ensembles of thousands of trajectories at once.

Implementation of Two-Component Time-Dependent Density Functional Theory in TURBOMOLE

Michael Kühn and Florian Weigend [Karlsruher Institut für Technologie]

J. Chem. Theor. and Comp, **9**, 5341–5348, 2013.

We report the efficient implementation of a two-component time-dependent density functional theory proposed by Wang et al. (Wang, F.; Ziegler, T.; van Lenthe, E.; van Gisbergen, S.; Baerends, E. J. *J. Chem. Phys.* **2005**, *122*, 204103) that accounts for spin–orbit effects on excitations of closed-shell systems by employing a noncollinear exchange–correlation kernel. In contrast to the aforementioned implementation, our method is based on two-component effective core potentials as well as Gaussian-type basis functions.

Leveraging Symmetries of Static Atomic Multipole Electrostatics in Molecular Dynamics Simulations

Tristan Bereau[University of Basel], Christian Kramer, and Markus Meuwly

J. Chem. Theor. and Comp, **9**, 5450–5459, 2013.

Multipole (MTP) electrostatics provides the means to describe anisotropic interactions in a rigorous and systematic manner. A number of earlier molecular dynamics (MD) implementations have increasingly relied on the use of molecular symmetry to reduce the (possibly large) number of MTP interactions. Here, we present a CHARMM implementation of MTP electrostatics in terms of spherical harmonics. By relying on a systematic set of reference-axis systems tailored to various chemical environments, we obtain an implementation that is both efficient and scalable for (bio)molecular systems.

Comparative or Homology Modeling

Homology modeling and docking studies of BjGL, a novel (+) gamma-lactamase from *Bradyrhizobium japonicum*

Dawei Song, Shaozhou Zhu, Xingzhou Li, Guojun Zheng [Beijing University of Chemical Technology]

J. Mol.Graph. and Mod., **47,** 1-7, 2014.

(+) Gamma-lactamases are enantioselective hydrolysis enzymes that can be used to produce optically pure (−) gamma-lactam, an important pharmaceutical intermediate for the anti-AIDS drug Abacavir. In this study, homology modeling and molecular dynamic simulation studies of a 3D homology model of BjGL, a novel (+) gamma-lactamase from *Bradyrhizobium japonicum*, were constructed and refined.

Comparative or Homology Modeling (Cont'd)

Some insights into the binding mechanism of the $GABA_A$ receptor: a combined docking and MM-GBSA study

Hong-Bo Xie, Yu Sha, Jian Wang, Mao-Sheng Cheng [Shenyang Pharmaceutical University]

J. Mol.Mod., **19,** 5489-5500, 2013.

Gamma-aminobutyric type A receptor ($GABA_AR$) is a member of the Cys-loop family of pentameric ligand gated ion channels (pLGICs). It has been identified as a key target for many clinical drugs. In the present study, we construct the structure of human $2\alpha_1 2\beta_2\gamma_2$ $GABA_AR$ using a homology modeling method. The structures of ten benzodiazepine type drugs and two non-benzodiazepine type drugs were then docked into the potential benzodiazepine binding site on the $GABA_AR$. Byanalyzing the docking results, the critical residues His102 (α_1), Phe77 (γ_2) and Phe100 (α_1) were identified in the binding site. To gain insight into the binding affinity, molecular dynamics (MD) simulations were performed for all the receptor–ligand complexes.

Protein docking using case-based reasoning

Anisah W. Ghoorah, Marie-Dominique Devignes, Malika Smaïl-Tabbone and David W. Ritchie[INRIA,LORIA, Campus Scientifique]

Proteins: Stru. Fun. & Bioinf., **81**, 2150–2158, 2013.

Protein docking algorithms aim to calculate the three-dimensional (3D) structure of a protein complex starting from its unbound components. Although *ab initio* docking algorithms are improving, there is a growing need to use homology modeling techniques to exploit the rapidly increasing volumes of structural information that now exist. To model 3D protein complexes by domain–domain homology, we have developed a case-based reasoning approach called KBDOCK which systematically identifies and reuses domain family binding sites from our database of nonredundant DDIs.

Kink Characterization and Modeling in Transmembrane Protein Structures

Tim Werner and W. Bret Church [The University of Sydney]

J.Chem. Infor. and Mod. **53**, 2926–2936, 2013.

The work entailed a thorough analysis of the available high resolution membrane protein structures, concomitantly demonstrating the complexity of the structural considerations for kink prediction. Furthermore, our results indicate that there are systematic and significant differences in the sequence as well as the structural environment between kinked and nonkinked transmembrane helices. To the best of our knowledge, we are reporting a method for modeling kinks for the first time.

The Molecular Basis for the Selectivity of Tadalafil toward Phosphodiesterase 5 and 6: A Modeling Study

Yi-You Huang, Zhe Li, Ying-Hong Cai, Ling-Jun Feng, Yinuo Wu, Xingshu Li, and Hai-Bin Luo[Sun Yat-Sen University]

J.Chem. Infor. and Mod. **53**, 3044-3053, 2013.

A!

Great attention has been paid to the clinical significance of phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil, tadalafil, and vardenafil widely used for erectile dysfunction. The present work reveals that tadalafil exhibits a less negative predicted binding free energy of −35.21 kcal/mol with PDE6 compared with the value of −41.12 kcal/mol for PDE5, which suggests that tadalafil prefers PDE5 rather than PDE6 and confers a high selectivity for PDE5 versus PDE6. The binding free energy results for tadalafil were consistent with external bioassay studies (IC_{50} = 5100 and 5 nM toward PDE6 and

PDE5, respectively).

Ligand Docking

Heterogeneous Classifier Fusion for Ligand-Based Virtual Screening: Or, How Decision Making by Committee Can Be a Good Thing

Sereina Riniker, Nikolas Fechner, and Gregory A. Landrum [Novartis Campus]

J.Chem. Infor. and Mod. **53**, 2829–2836, 2013.

The concept of data fusion - the combination of information from different sources describing the same object with the expectation to generate a more accurate representation - has found application in a very broad range of disciplines. In the context of ligand-based virtual screening (VS), data fusion has been applied to combine knowledge from either different active molecules or different fingerprints to improve similarity search performance. Machine-learning (ML) methods based on fusion of multiple homogeneous classifiers, in particular random forests, have also been widely applied in the ML literature. Here, we investigate heterogeneous classifier fusion for ligand-based VS using three different ML methods, RF, naïve Bayes (NB), and logistic regression (LR), with four 2D fingerprints, atom pairs, topological torsions, RDKit fingerprint, and circular fingerprint.

Energetic and Dynamic Aspects of the Affinity Maturation Process: Characterizing Improved Variants from the Bevacizumab Antibody with Molecular Simulations

Dario Corrada and Giorgio Colombo [Istituto di Chimica del Riconoscimento Molecolare − Consiglio Nazionale delle Ricerche (CNR-ICRM)]

J.Chem. Infor. and Mod. **53**, 2937–2950, 2013.

A! & S!

Antibody affinity maturation is one of the fundamental processes of immune defense against invading pathogens. From the biological point of view, the clonal selection hypothesis represents the most accepted mechanism to explain how mutations increasing the affinity for target antigens are introduced and selected in antibody molecules. However, understanding at the molecular level how protein modifications, such as point mutation, can modify and modulate the affinity of an antibody for its antigen is still a major open issue in molecular biology. In this paper, we address various aspects of this problem by analyzing and comparing atomistic simulations of 17 variants of the bevacizumab antibody, all directed against the common target protein VEGF-A.

Predictions of BuChE Inhibitors Using Support Vector Machine and Naive Bayesian Classification Techniques in Drug Discovery

Jiansong Fang, Ranyao Yang, Li Gao, Dan Zhou, Shengqian Yang, Ai-lin Liu[Chinese Academy of Medical Sciences and Peking Union Medical College], and Guan-hua Du

J.Chem. Infor. and Mod. **53**, 3009-3020, 2013.

Butyrylcholinesterase (BuChE, EC 3.1.1.8) is an important pharmacological target for Alzheimer's disease (AD) treatment. However, the currently available BuChE inhibitor screening assays are expensive, labor-intensive, and compound-dependent. It is necessary to develop robust in silico methods to predict the activities of BuChE inhibitors for the lead identification. In this investigation, support vector machine (SVM) models and naive Bayesian models were built to discriminate BuChE inhibitors (BuChEIs) from the noninhibitors.

Ligand Docking (Cont'd)

Visually Interpretable Models of Kinase Selectivity Related Features Derived from Field-Based Proteochemometrics

Vigneshwari Subramanian, Peteris Prusis, Lars-Olof Pietilä, Henri Xhaard, and Gerd Wohlfahrt [Orion Pharma, Orionintie 1]

J.Chem. Infor. and Mod. **53**, 3021-3030, 2013.

S!

To support the design of more selective inhibitors with fewer side effects or with altered target profiles for improved efficacy, we developed a method combining ligand- and receptor-based information. Conventional QSAR models enable one to study the interactions of multiple ligands toward a single protein target, but in order to understand the interactions between multiple ligands and multiple proteins, we have used proteochemometrics, a multivariate statistics method that aims to combine and correlate both ligand and protein descriptions with affinity to receptors.

Defining the limits of homology modeling in information-driven protein docking

J. P. G. L. M. Rodrigues, A. S. J. Melquiond, E. Karaca, M. Trellet, M. van Dijk, G. C. P. van Zundert, C. Schmitz, S. J. de Vries, A. Bordogna, L. Bonati, P. L. Kastritis and Alexandre M. J. J. Bonvin[Utrecht University]

Proteins: Stru. Fun. & Bioinf., **81**, 2119–2128, 2013.

While various experimental and computational techniques can be used to retrieve information about the binding mode, the availability of three-dimensional structures of the interacting partners remains a limiting factor. Fortunately, the wealth of structural information gathered by large-scale initiatives allows for homology-based modeling of a significant fraction of the protein universe. Defining the limits of information-driven docking based on such homology models is therefore highly relevant. Here we show, using previous CAPRI targets, that out of a variety of measures, the global sequence identity between template and target is a simple but reliable predictor of the achievable quality of the docking models.

Exact Ligand Solid Angles

Jenna A. Bilbrey, Arianna H. Kazez, Jason Locklin, and Wesley D. Allen [University of Georgia]

J. Chem. Theor. and Comp, **9**, 5734–5744, 2013.

Steric demands of a ligand can be quantified by the area occluded by the ligand on the surface of an encompassing sphere centered at the metal atom. When viewed as solid spheres illuminated by the metal center, the ligand atoms generally cast a very complicated collective shadow onto the encompassing sphere, causing mathematical difficulties in computing the subtended solid angle. Herein, an exact, analytic solution to the ligand solid angle integration problem is presented based on a line integral around the multisegmented perimeter of the ligand shadow. The solution, which is valid for any ligand bound to any metal center, provides an excellent method for analyzing geometric structures from quantumchemical computations or X-ray crystallography.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 47, December, 2013.

1-7 **Homology modeling and docking studies of BjGL, a novel (+) gamma-lactamase from *Bradyrhizobium japonicum*** ,Dawei Song, Shaozhou Zhu, Xingzhou Li, Guojun Zheng [Beijing University of Chemical Technology]

See Applications / Homology Modeling.

8-17 **Insight into the interaction between DNA bases and defective graphenes: Covalent or non-covalent** ,Zhenfeng Xu, Biswa Ranjan Meher, Darnashley Eustache, Yixuan Wang [Albany State University]

See Applications / Protein-Nucleic acids.

18-24 **P1 and P1′ *para*-fluoro phenyl groups show enhanced binding and favorable predicted pharmacological properties: Structure-based virtual screening of extended lopinavir analogs against multi-drug resistant HIV-1 protease** ,Ravikiran S. Yedidi, Zhigang Liu, Iulia A. Kovari, Patrick M. Woster, Ladislau C. Kovari[Wayne State University]

See Applications / Medicinal Chemmistry and Drug Design.

25-36 **Efficient prediction of protein conformational pathways based on the hybrid elastic network model** Sangjae Seo, Yunho Jang, Pengfei Qian, Wing Kam Liu, Jae-Boong Choi, Byeong Soo Lim, Moon Ki Kim [Sungkyunkwan University]

See Applications / Protein Confirmational Analysis.

Journal of Computational Chemistry, 34 (32), December 2013.

2757–2770 **Rapid parameterization of small molecules using the force field toolkit ,**Christopher G. Mayne ,Jan Saam,Klaus Schulten , Emad Tajkhorshid [University of Illinois at Urbana-Champaign],James C. Gumbart,

See Methodology / Potentilas and Parameters.

2771–2773 **A new set of bending T_d symmetry coordinates for MX_4 molecules ,**David Schmidling [Bronx Community College of The City University of New York]

The conventional set of T_d symmetry coordinates for the bending modes of MX_4 molecules can lead to ambiguous geometries when displacements from equilibrium are large. It is proposed here to use internal coordinates that are haversines of the bending angles divided by their sum.

2774–2786 **Elucidating protein secondary structure with circular dichroism and a neural network,** Vincent Hall, Anthony Nash, Evor Hines, Alison Rodger[University of Warwick]

See Applications / Protein Secondary Structure.

2787–2795 **Kinetic energy decomposition scheme based on information theory ,**Yutaka Imamura, Jun Suzuki, Hiromi Nakai [Advanced Institute for Computational Science, RIKEN]

We proposed a novel kinetic energy decomposition analysis based on information theory. Since the Hirshfeld partitioning for electron densities can be formulated in terms of Kullback–Leibler information deficiency in information theory, a similar partitioning for kinetic energy densities was newly proposed.

2796–2805 **Refinement of the application of the GROMOS 54A7 force field to β-peptides ,**Zhixiong Lin, Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

See Applications / Protein Confirmational Analysis.

2806–2815 **Chemical mechanism of surface-enhanced raman scattering spectrum of pyridine adsorbed on Ag cluster: *Ab initio* molecular dynamics approach ,**Jen-Ping Su, Yung-Ting Lee, Shao-Yu Lu, Jyh Shing Lin [Tamkang University]

See Applications / Surface, Catalysts, Materials subject.

2816–2833 **QuanPol: A full spectrum and seamless QM/MM program ,**Nandun M. Thellamurege, Dejun Si, Fengchao Cui, Hongbo Zhu, Rui Lai, Hui Li [University of Nebraska-Lincoln]

See Methodology / QM and QM/MM.

Journal of Computational Chemistry, 35 (1), January 2014.

1–17 **Geometrical and optical benchmarking of copper guanidine–quinoline complexes: Insights from TD-DFT and many-body perturbation theory** ,Anton Jesser, Martin Rohrmüller, Wolf Gero Schmidt, Sonja Herres-Pawlis Ludwig-Maximilians-Universität München]

We report a comprehensive computational benchmarking of the structural and optical properties of a bis(chelate) copper(I) guanidine–quinoline complex. Using various (TD-)DFT flavors a strong influence of the basis set is found.

18–29 **Toward force fields for atomistic simulations of iridium-containing complexes ,**Franziska D. Hofmann, Michael Devereux, Andreas Pfaltz, Markus Meuwly [University of Basel]

The structural and energetic characterization of metal complexes is important in catalysis and photochemical applications. Here, we present an empirical force field based on valence bond theory applicable to a range of octahedral Ir(III) complexes with different coordinating ligands, including iridium complexes with a chiral P,N ligand.

30–38 **Multi-level quantum monte Carlo wave functions for complex reactions: The decomposition of α-hydroxy-dimethylnitrosamine ,**Francesco FracchiaClaudia Filippi [Università di Ferrara],Claudio Amovilli

We present here several novel features of our recently proposed Jastrow linear generalized valence bond (J-LGVB) wave functions, which allow a consistently accurate description of complex potential energy surfaces (PES) of medium-large systems within quantum MonteCarlo (QMC).

39–50 **Adaptive lambda square dynamics simulation: An efficient conformational sampling method for biomolecules ,**Jinzen Ikebe, Shun Sakuraba, Hidetoshi Kono[Japan Atomic Energy Agency,]

See Applications / Protein Confirmational Analysis.

51–61 **Structural, spectroscopic aspects, and electronic properties of $(TiO_2)n$clusters: A study based on the use of natural algorithms in association with quantum chemical methods ,**Soumya Ganguly Neogi, Pinaki Chaudhury [University of Calcutta]

In this article, we propose a stochastic search-based method, namely genetic algorithm (GA) and simulated annealing (SA) in conjunction with density functional theory (DFT) to evaluate global and local minimum structures of $(TiO_2)n$ clusters with n = 1–12.

62–69 **Incorporating the excluded solvent volume and surface charges for computing solvation free energy** Pei-Kun Yang [I-SHOU University]

See Methodology / Solvent Energy.

70–81 **Small molecule-mediated control of hydroxyapatite growth: Free energy calculations benchmarked to density functional theory ,**Zhijun Xu, Yang Yang, Ziqiu Wang,Donald Mkhonto, Cheng Shang, Zhi-Pan Liu, Qiang Cui, Nita Sahai[University of Akron]

See Methodology / Free Energy Perturbations.

82–93 **KiSThelP: A program to predict thermodynamic properties and rate constants from quantum chemistry results ,**Sébastien Canneaux ,Frédéric Bohr ,Eric Henon [University of Reims Champagne-Ardenne]

Kinetic and Statistical Thermodynamical Package (KiSThelP) is a cross-platform free open-source program developed to estimate molecular and reaction properties from electronic structure data. To date, three computational chemistry software formats are supported (Gaussian, GAMESS, and NWChem). Kassel-Marcus (RRKM) rate constants, for elementary reactions with well-defined barriers. KiSThelP is intended as a working tool both for the general public and also for more expert users.

Journal of Molecular Modeling, 19 (12), December, 2013.

5135-5142 **Prediction of thermodynamically reversible hydrogen storage reactions utilizing Ca–M(M = Li, Na, K)–B–H systems: a first-principles study ,**Yajuan Guo, Ying Ren, Haishun Wu [Shanxi Normal University], Jianfeng Jia

In this study, $Ca(BH_4)_2$ was predicted to form a destabilized system when it was mixed with $LiBH_4$, $NaBH_4$, or KBH_4. The release of hydrogen from $Ca(BH_4)_2$ was predicted to proceed viatwo competing reaction pathways (leading to CaB_6 and CaH_2 or $CaB_{12}H_{12}$ and CaH_2) that were found to have almost equal free energies.

5143-5152 **Stability and properties of the two-dimensional hexagonal boron nitride monolayer functionalized by hydroxyl (OH) radicals: a theoretical study** ,Hong-mei Wang, Yue-jie Liu, Hong-xia Wang, Jing-xiang Zhao, Qing-hai Cai, Xuan-zhang Wang[Harbin Normal University]

Motivated by the great advance in graphene hydroxide—a versatile material with various applications—we performed density functional theory (DFT) calculations to study the functionalization of the two-dimensional hexagonal boron nitride (*h*-BN) sheet with hydroxyl (OH) radicals, which has been achieved experimentally recently.

5153-5158 **Penta- and heteropentadienyl ligands coordinated to beryllium** ,Sharity Morales-Meza, M. Esther Sanchez-Castro, Mario Sanchez

In this work we have performed a systematic study of new organometallic complexes containing penta- and heteropentadienyl ($CH_2CHCHCHX$, X = CH_2, O, NH, S) ligands coordinated to beryllium.

5159-5170 **First-principles study of the structural transformation, electronic structure, and optical properties of crystalline 2,6-diamino-3,5-dinitropyrazine-1-oxide under high pressure** ,Qiong Wu, Chunhong Yang, Yong Pan, Fang Xiang, Zhichao Liu, Weihua Zhu[Nanjing University of Science and Technology], Heming Xiao

Periodic first-principles calculations have been performed to study the effect of high pressure on the geometric, electronic, and absorption properties of 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105) under hydrostatic pressures of 0–50 GPa.

5187-5198 **Insight into the molecular mechanism about lowered dihydrofolate binding affinity to dihydrofolate reductase-like 1 (DHFRL1)** ,Jian Gao, Wei Cui, Yuguo Du, Mingjuan Ji [University of Chinese Academy of Sciences]

See Applications / Ligand Binding.

5199-5211 **Probing the electronic structures and properties of neutral and charged arsenic sulfides ($As_nS^{(-1,0,+1)}$, $n = 1–7$) using Gaussian-3 theory** ,Jucai Yang[Inner Mongolia University of Technology], Yali Kang, Xi Wang, Xue Bai

The structures and energies of neutral and charged arsenic sulfides $As_nS^{(-1,0,+1)}$ ($n = 1–7$) were systematically investigated using the G3 method. The bonding properties and the stabilities of As_nS and their ions were discussed.

5213-5223 **Highlighting a $\pi–\pi$ interaction: a protein modeling and molecular dynamics simulation study on *Anopheles gambiae*glutathione S-transferase 1-2** ,Yan Wang, Qing-Chuan Zheng, Ji-Long Zhang, Ying-Lu Cui, Qiao Xue, Hong-Xing Zhang[Jilin University]

See Applications / Protein Confirmational Analysis.

5225-5235 **Molecular docking of thiamine reveals similarity in binding properties between the prion protein and other thiamine-binding proteins ,**Nataraj S. Pagadala[University of Alberta], Trent C. Bjorndahl, Nikolay Blinov, Andriy Kovalenko, David S. Wishart

See Applications / Ligand Binding.

5237-5244 **Coupling of mechanical and electronic properties of carbon nanotubes ,**Dahiyana Cristancho, Laura Benitez, Jorge M. Seminario [Texas A&M University]

Because of the potential importance of carbon nanotubes (CNT) in renewable energy and other fields, molecular orbital ab initio calculations are used to study the relation between mechanical and electronic properties of such structures.

5245-5255 **Exploration of various electronic properties along the reaction coordinate for hydration of Pt(II) and Ru(II) complexes; the CCSD, MPx, and DFT computational study ,**Jaroslav V. Burda[Charles University], Zdeněk Futera, Zdeněk Chval

In the study behavior of molecular electrostatic potential, averaged local ionization energy, and reaction electronic flux along the reaction coordinate of hydration process of three representative Ru(II) and Pt(II) complexes were explored using both post-HF and DFT quantum chemical approximations.

5257-5266 **Investigation of the binding network of IGF-I on the cavity surface of IGFBP4** ,Xin Chen[Henan University], Shuyan Zhu, Danhui Duan, Tao Wu, Qi Wang

See Applications / Ligand Binding.

5267-5276 **New insights into the stability of alkenes and alkynes, fluoro-substituted or not: a DFT, G4, QTAIM and GVB study**, Caio Lima Firme [Federal University of Rio Grande do Norte]

Many undergraduate organic chemistry books do not agree with the order of relative stability of alkenes towards hydrogenation reactions. Although they ascribe the stability of alkenes to the number and spatial position of the alkyl groups attached to the vinyl carbon atoms, results from the quantum theory of atoms in molecules indicate that the influence of an alkyl substituent on the stability of unsaturated hydrocarbons arises

from the slight removal of electron density of the π bond, not from donation of their charge density to unsaturated carbon atoms as stated in many text books.

5277-5291 **Density functional theoretical study on the preferential selectivity of macrocyclic dicyclohexano-18-crown-6 for Sr^{+2} ion over Th^{+4} ion during extraction from an aqueous phase to organic phases with different dielectric constants ,**A. Boda, J. M. Joshi, Sk. M. Ali, K. T. Shenoy, S. K. Ghosh

The preferential selectivity of dicyclohexano-18-crown-6 (DCH18C6) for bivalent Sr^{+2} ion over tetravalent Th^{+4} ion was investigated using generalized gradient approximated (GGA) BP86 and thehybrid B3LYP density functional, employing split valence plus polarization (SV(P)) and triple-zeta valence plus polarization (TZVP) basis sets in conjunction with the COSMO (conductor-like screening model) solvation approach.

5293-5299 **Stacking and hydrogen bond interactions between adenine and gallic acid ,**Isidro Lorenzo, Ana M. Graña[Universidade de Vigo]

We have performed DFT and DFT-SAPT calculations on dimers of gallic acid, the model system for plant polyphenols, and the DNA base adenine. These dimers were selected for this study as they exhibit simultaneously hydrogen bonds and stacking interactions and it allows to quantify the relative values of these interactions.

5301-5216 **Structural analysis and molecular dynamics simulations of novel δ-endotoxin*Cry*1Id from *Bacillus thuringiensis* to pave the way for development of novel fusion proteins against insect pests of crops** ,Budheswar Dehury, Mousumi Sahu, Jagajjit Sahu, Kishore Sarma, Priyabrata Sen, Mahendra K. Modi, Madhumita Barooah [Assam Agricultural University], Manabendra Dutta Choudhury

See Applications / Protein Confirmational Analysis.

5317-5325 **Structure-property relationships for three indoline dyes used in dye-sensitized solar cells: TDDFT study of visible absorption and photoinduced charge-transfer processes ,**Huixing Li, Maodu Chen [Dalian University of Technology]

The electronic structures of three D-A-π-A indoline dyes (WS-2, WS-6, and WS-11) used in dye-sensitized solar cells (DSSCs) were studied by performing quantum chemistry calculations.

5327-5341 **Changes in ligating abilities of the singlet and triplet states of normal, abnormal and remote N-heterocyclic carbenes depending on their aromaticities** ,Resul Sevinçek, Hande Karabıyık[Dokuz Eylül University], Hasan Karabıyık

Quantum chemical calculations at B3LYP/aug-cc-pVTZ level about singlet N-heterocyclic carbene (NHC) ligands, imidazol-2-ylidene, imidazol-4-ylidene, pyrazol-3-ylidene and pyrazol-4-ylidene, and their protonated analogues show that they are considerably aromatic except for pyrazol-3-ylidene. This result is experimentally verified by approximately five thousand NHC transition metal complexes retrieved from the Cambridge Structural Database (CSD).

5343-5354 **Electronic, ductile, phase transition and mechanical properties of Lu-monopnictides under high pressures** ,Dinesh C. Gupta[Jiwaji University], Idris Hamid Bhat

The structural, elastic and electronic properties of lutatium-pnictides (LuN, LuP, LuAs, LuSb, and LuBi) were analyzed by using full-potential linearized augmented plane wave within generalizedgradient approximation in the stable rock-salt structure (B1 phase) with space group Fm-3m and high-pressure CsCl structure (B2 phase) with space group Pm-3m.

5355-5365 **A DFT study on the thermal cracking of JP-10** ,Lei Yue, Hu-Jun Xie, Xiao-Mei Qin, Xiao-Xing Lu, Wen-Jun Fang

Density functional theory (DFT) calculations have been carried out to investigate the thermal cracking pathways of JP-10, a high energy density hydrocarbon fuel.

5367-5376 **A theoretical study on 1,5-diazido-3-nitrazapentane (DANP) and 1,7-diazido-2,4,6-trinitrazaheptane (DATNH): molecular and crystal structures, thermodynamic and detonation properties, and pyrolysis mechanism ,**Junqing Yang, Fang Wang, Jianying Zhang, Guixiang Wang, Xuedong Gong[Nanjing University of Science and Technology]

1,5-Diazido-3-nitrazapentane (DANP) and 1,7-diazido-2,4,6-trinitrazaheptane (DATNH) are two energetic plasticizers. To better understand them, a detailed theoretical investigation was carried out using density functional theory and molecular mechanics methods.

5377-5385 **Theoretical investigation on the mechanism and kinetics of the ring-opening polymerization of ε-caprolactone initiated by tin(II) alkoxides ,**ChanchaiSattayanon, Nawee Kungwan[Chiang Mai University], Winita Punyodom, Puttinan Meepowpan, Siriporn Jungsuttiwong

A theoretical investigation of the ring-opening polymerization (ROP) mechanism of ε-caprolactone (CL) with tin(II) alkoxide, $Sn(OR)_2$ initiators (R = *n*-C_4H_9, *i*-C_4H_9, *t*-C_4H_9, *n*-C_6H_{13}, *n*-C_8H_{17}) was studied. The density functional theory at B3LYP level was used to perform the modeled reactions.

5387-5395 **Revealing the nature of intermolecular interaction and configurational preference of the nonpolar molecular dimers $(H_2)_2$, $(N_2)_2$, and $(H_2)(N_2)$,**Tian Lu, Feiwu Chen [University of Science and Technology Beijing]

Understanding the nature of noncovalent interactions between nonpolar small molecules is not only theoretically interesting but also important for practical purposes. The interaction mechanism of three prototype dimers $(H_2)_2$, $(N_2)_2$, and $(H_2)(N_2)$ are investigated by state-of-the-art quantum chemistry calculations and energy decomposition analysis.

5396-5406 **A study of the solvent effect on the morphology of RDX crystal by molecular modeling method ,**Gang Chen, Mingzhu Xia[Nanjing University of Science and Technology], Wu Lei, Fengyun Wang, Xuedong Gong

Molecular dynamics simulations have been performed to investigate the effect of acetone solvent on the crystal morphology of RDX. The results show that the growth morphology of RDX crystal in vacuum is dominated by the (111), (020), (200), (002), and (210) faces using the BFDH laws, and (111) face is morphologically the most important.

5407-5422 **Mechanistic investigation of methanol to propene conversion catalyzed by H-beta zeolite: a two-layer ONIOM study ,**Yingxin Sun, Sheng Han[Shanghai Institute of Technology]

See Applications / Zeolites.

5423-5427 **Random sequential adsorption of trimers and hexamers** ,Michał Cieśla[Jagiellonian University], Jakub Barbasz

Adsorption of trimers and hexamers built of identical spheres was studied numerically using the random sequential adsorption (RSA) algorithm.

5429-5438 **Mechanisms on electrical breakdown strength increment of polyethylene by aromatic carbonyl compounds addition: a theoretical study** ,Hui Zhang[Harbin University of Science and Technology], Yan Shang, Xuan Wang, Hong Zhao, Baozhong Han, Zesheng Li

A theoretical investigation is accomplished on the mechanisms of electrical breakdown strengthincrement of polyethylene at the atomic and molecular levels. It is found that the addition of aromatic carbonyl compounds as voltage stabilizers is one of the important factors for increasing electrical breakdown strength of polyethylene, as the additives can trap hot electrons, obtain energy of hot electrons, and transform the aliphatic cation to relatively stable aromatic cation to prevent the degradation of the polyethylene matrix.

5439-5444 **An assessment of DFT methods for predicting the thermochemistry of ion-molecule reactions of group 14 elements (Si, Ge, Sn)** ,Igor S. Ignatyev, Manuel Montejo, Juan Jesús López González[University of Jaén]

Experimental mass-spectrometry data on thermochemistry of methide transfer reactions $(CH_3)_3M^+ + M'(CH_3)_4 \leftrightarrow M(CH_3)_4 + (CH_3)_3M'^+$ (M, M' = Si, Ge or Sn) and the formation energy of the $[(CH_3)_3Si\text{-}CH_3\text{-}Si(CH_3)_3]^+$ complex are used as benchmarks for DFT methods (B3LYP, BMK, M06L, and ωB97XD). G2 and G3 theory methods are also used for the prediction of thermochemical data.

5445-5456 **Modeling the scavenging activity of ellagic acid and its methyl derivatives towards hydroxyl, methoxy, and nitrogen dioxide radicals** ,Manish Kumar Tiwari, Phool Chand Mishra [Banaras Hindu University]

The reaction mechanisms involved in the scavenging of hydroxyl ($OH^{\cdot}$), methoxy ($OCH_3^{\cdot}$), andnitrogen dioxide ($NO_2^{\cdot}$) radicals by ellagic acid and its monomethyl and dimethyl derivatives were investigated using the transition state theory and density functional theory.

5457-5467 **Evaluation of density functional methods on the geometric and energetic descriptions of species involved in Cu^+-promoted catalysis ,Carlos E. P. Bernardo, Nicholas P. Bauman, Piotr Piecuch, Pedro J. Silva[University Fernando Pessoa]**

We have evaluated the performance of 15 density functionals of diverse complexity on the geometry optimization and energetic evaluation of model reaction steps present in the proposed reaction mechanisms of Cu(I)-catalyzed indole synthesis and click chemistry of iodoalkynes and azides.

5469-5477 **A refined parameterization of the analytical Cd–Zn–Te bond-order potential** ,Donald K. Ward[Sandia National Laboratories], Xiaowang Zhou, Bryan M. Wong, F. Patrick Doty

This paper reports an updated parameterization for a CdTe bond order potential. The original potential is a rigorously parameterized analytical bond order potential for ternary the Cd–Zn–Te systems.

5539-5543 **Molecular dynamics approach to investigate the coupling of the hydrophilic–lipophilic balance with the configuration distribution function in biosurfactant-based emulsions** ,Melissa Álvarez Vanegas, Angie Macías Lozano, Vanessa Núñez Vélez, Nathalia Garcés Ferreira,Harold Castro Barrera, Oscar Álvarez Solano, Andrés Fernando González Barrios[Universidad de los Andes]

See Applications / Membrance protein and lipid-peptide interaction.

5545-5559 **QM-MM simulations on p53-DNA complex: a study of hot spot and rescue mutants ,**Shruti Koulgi, Archana Achalere, Neeru Sharma, Uddhavesh Sonavane, Rajendra Joshi[Pune University Campus]

See Applications / Nucleic Acids.

5561-5568 **Theoretical studies of the interaction between influenza virus hemagglutinin and its small molecule ligands ,** Deshou Song, Hanhong Xu[South China Agricultural University], Shuwen Liu

See Applications / Medicinal Chemmistry and Drug Design.

5569-5577 **Structures, spectroscopic and thermodynamic properties of U_2O_n ($n = 0 \sim 2, 4$) molecules: a density functional theory study** ,Peng Li, Wen-Xia Niu, Tao Gao[Sichuan University], Fan Wang, Ting-Ting Jia, Da-Qiao Meng, Gan Li

The equilibrium structures, spectroscopic and thermodynamic parameters [entropy (S), internal energy (E), heat capacity (C_p)] of U_2, U_2O, U_2O_2 and U_2O_4 uranium oxide molecules were investigated systematically using density functional theory (DFT).

5579-5586 **From pure C_{36} fullerene to cagelike nanocluster: a density functional study** ,Shu-Wei Tang, Feng-Di Wang, Yu-Han Li, Fang Wang, Shao-Bin Yang, Hao Sun, Ying-Fei Chang[Northeast Normal University],Rong-Shun Wang

The geometrical structures, energetics properties, and aromaticity of $C_{36-n}Si_n$ ($n \leq 18$) fullerene-based clusters were studied using density functional theory calculations. The geometries of $C_{36-n}Si_n$ clusters undergo strong structural deformation with the increase of Si substitution.

5587-5599 **In-silico screening of cancer associated mutation on PLK1 protein and its structural consequences** ,Balu Kamaraj, Vidya Rajendran, Rao Sethumadhavan, Rituraj Purohit

See Applications / Medicinal Chemmistry and Drug Design.

5601-5610 **(Super)alkali atoms interacting with the σ electron cloud: a novel interaction mode triggers large nonlinear optical response of $M@P_4$ and $M@C_3H_6$ (M=Li, Na, K and Li_3O)** ,Xingang Zhao, Guangtao Yu[Jilin University], Xuri Huang, Wei Chen, Min Niu

Under high-level ab initio calculations, the geometrical structures and nonlinear optical properties of $M@P_4$ (M=Li, Na, K and Li_3O) and $M@C_3H_6$ (M=Li and Li_3O) were investigated; all were found to exhibit considerable first hyperpolarizabilities (18110, 1440, 22490, 50487, 2757 and 31776 au, respectively).

5611-5624 **Molecular interactions of alcohols with zeolite BEA and MOR frameworks ,**Kai Stückenschneider, Juliane Merz[TU Dortmund University], Gerhard Schembecker

In this study, the adsorption of C1–C4 alcohols in BEA and MOR was investigated using density functional theory (DFT). Calculated adsorption geometries and the corresponding energies of the designed cluster models were comparable to periodic calculations, and the adsorption energies were in the same range as the corresponding computational and experimental values reported in the literature for zeolite MFI.

5625-5632 **Cooperativity between fluorine-centered halogen bonds: investigation of substituent effects** Mehdi D. Esraili[University of Maragheh], Fariba Mohammadian-Sabet, Parvin Esmailpour, Mohammad Solimannejad

This article analyzes the substitution effects on cooperativity between fluorin-centered halogenbonds in NCF · · · NCF · · · NCX and CNF · · · CNF · · · CNX complexes, where X = H, F, Cl, CN, OH, and NH_2.

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4. ADDRESSES OF PRINCIPAL AUTHORS

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1. APPLICATIONS

1.1. *Small Molecules*

Medicinal Chemistry and Drug Design

Design, modification and 3D QSAR studies of novel naphthalin-containing pyrazoline derivatives with/without thiourea skeleton as anticancer agents

Wen Yang, Yang Hu, Yu-Shun Yang, Fei Zhang, Yan-Bin Zhang, Xiao-Liang Wang, Jian-Feng Tang, Wei-Qing Zhong, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med.Chem., **21**, 1050-1063, 2013.

Two series of novel naphthalin-containing pyrazoline derivatives **C1**–**C14** and **D1–D14** have been synthesized and evaluated for their EGFR/HER-2 inhibitory and anti-proliferation activities. Compound **D14** displayed the most potent activity against EGFR and A549 cell line (IC_{50} = 0.05 μM and GI_{50} = 0.11 μM), being comparable with the positive control Erlotinib (IC_{50} = 0.03 μM and GI_{50} = 0.03 μM) and more potent than our previous compounds **C0–A** (IC_{50} = 5.31 μM and GI_{50} = 33.47 μM) and **C0–B** (IC_{50} = 0.09 μM and GI_{50} = 0.34 μM).

The interactions and recognition of cyclic peptide mimetics of Tat with HIV-1 TAR RNA: a molecular dynamics simulation study

Chun Hua Li, Zhi Cheng Zuo, Ji Guo Su, Xian Jin Xu & Cun Xin Wang [Beijing University of Technology]

J. Biomol. Stru. and Dyn., **31**, 276-287, 2013.

The interaction of HIV-1 trans-activator protein Tat with its cognate trans-activation response element (TAR) RNA is critical for viral transcription and replication. Therefore, it has long been considered as an attractive target for the development of antiviral compounds. Recently, the conformationally constrained cyclic peptide mimetics of Tat have been tested to be a promising family of lead peptides. Here, we focused on two representative cyclic peptides termed as L-22 and KP-Z-41, both of which exhibit excellent inhibitory potency against Tat and TAR interaction. By means of molecular dynamics simulations, we obtained a detailed picture of the interactions between them and HIV-1 TAR RNA.

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Medicinal Chemistry and Drug Design (Cont'd)

Structure-based design of nitrogen-linked macrocyclic kinase inhibitors leading to the clinical candidate SB1317/TG02, a potent inhibitor of cyclin dependant kinases (CDKs), Janus kinase 2 (JAK2), and Fms-like tyrosine kinase-3 (FLT3)

Anders Poulsen [S*BIO Pte Ltd], Anthony William, Stéphanie Blanchard, Harish Nagaraj, Meredith Williams, Haishan Wang, Angeline Lee, Eric Sun, Ee-Ling Teo, Evelyn Tan, Kee Chuan Goh, Brian Dymock

J. Mol.Mod., **19,** 119-130, 2013.

A high-throughput screen against Aurora A kinase revealed several promising submicromolar pyrimidine-aniline leads. The bioactive conformation found by docking these leads into the Aurora A ATP-binding site had a semicircular shape. Macrocycle formation was proposed to achieve novelty and selectivity via ring-closing metathesis of a diene precursor. The nature of the optimal linker and its size was directed by docking. In a kinase panel screen, selected macrocycles were active on other kinase targets, mainly FLT3, JAK2, and CDKs. These compounds then became leads in a CDK/FLT3/JAK2 inhibitor project. Macrocycles with a basic nitrogen in the linker form a salt bridge with Asp86 in CDK2 and Asp698 in FLT3. Interaction with this residue explains the observed selectivity.

Structural and chemical basis for enhanced affinity to a series of mycobacterial thymidine monophosphate kinase inhibitors: fragment-based QSAR and QM/MM docking studies

Renata V. Bueno, Ney R. Toledo, Bruno J. Neves, Rodolpho C. Braga, Carolina H. Andrade [Universidade Federal de Goiás]

J. Mol.Mod., **19,** 179-192, 2013.

Tuberculosis (TB) still remains one of the most deadly infectious diseases. Mycobacterium tuberculosis thymidine monophosphate kinase (TMPKmt) has emerged as an attractive molecular target for the design of a novel class of anti-TB agents since blocking it will affect the pathways involved in DNA replication. Aiming at shedding some light on structural and chemical features that are important for the affinity of thymidine derivatives to TMPKmt, we have employed a special fragment-based method to develop robust quantitative structure-activity relationship models for a large and chemically diverse series of thymidine-based analogues.

A plausible explanation for enhanced bioavailability of P-gp substrates in presence of piperine: simulation for next generation of P-gp inhibitors

Durg Vijay Singh, Madan M. Godbole, Krishna Misra [Center of Biomedical Magnetic Resonance, Lucknow]

J. Mol.Mod., **19,** 227-238, 2013.

P-glycoprotein (P-gp) has a major role to play in drug pharmacokinetics and pharmacodynamics, since it effluxes many cytotoxic hydrophobic anticancer drugs from gastrointestinal tract, brain, liver and kidney. Piperine is known to enhance the bioavailability of curcumin, as a substrate of P-gp by at least 2000 %. In the present study, piperine up to 100 μM has not shown observable cytotoxic effect on MDCK cell line, and it has been shown to accumulate rhodamine by fluorescence microscopy and fluorescent activated cell sorter in MDCK cells.

Medicinal Chemistry and Drug Design (Cont'd)

Discovery of novel low-molecular-weight HIV-1 inhibitors interacting with cyclophilin A using in silico screening and biological evaluations

Yu-Shi Tian, Chris Verathamjamras, Norihito Kawashita, Kousuke Okamoto, Teruo Yasunaga, Kazuyoshi Ikuta, Masanori Kameoka, Tatsuya Takagi [Osaka University]

J. Mol.Mod., **19,** 465-475, 2013.

Cyclophilin A has attracted attention recently as a new target of anti-human immunodeficiency virus type 1 (HIV-1) drugs. However, so far no drug against HIV-1 infection exhibiting this mechanism of action has been approved. To identify new potent candidates for inhibitors, we performed in silico screening of a commercial database of more than 1,300 drug-like compounds by using receptor-based docking studies. The candidates selected from docking studies were subsequently tested using biological assays to assess anti-HIV activities. As a result, two compounds were identified as the most active.

Discovery of potent inhibitors for interleukin-2-inducible T-cell kinase: structure-based virtual screening and molecular dynamics simulation approaches

Chandrasekaran Meganathan, Sugunadevi Sakkiah, Yuno Lee, Jayavelu Venkat Narayanan, Keun Woo Lee [Gyeongsang National University]

J. Mol.Mod., **19,** 715-726, 2013.

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In our study, a structure-based virtual screening study was conducted to identify potent ITK inhibitors, as ITK is considered to play an important role in the treatment of inflammatory diseases. We developed a structure-based pharmacophore model using the crystal structure (PDB ID: 3MJ2) of ITK complexed with BMS-50944. The most predictive model, SB-Hypo1, consisted of six features: three hydrogen-bond acceptors (HBA), one hydrogen-bond donor (HBD), one ring aromatic (RA), and one hydrophobic (HY). The statistical significance of SB-Hypo1 was validated using wide range of test set molecules and a decoy set.

Subpocket Analysis Method for Fragment-Based Drug Discovery

Tuomo Kalliokoski, Tjelvar S. G. Olsson, and Anna Vulpetti [Novartis Institutes for Biomedical Research]

J.Chem. Infor. and Mod. **53**, 131–141, 2013.

Although two binding sites might be dissimilar overall, they might still bind the same fragments if they share suitable subpockets. Information about shared subpockets can be therefore used in fragment-based drug design to suggest new fragments or to replace existing fragments within an already known compound. A novel computational method called SubCav is described which allows the similarity searching and alignment of subpockets from a PDB-wide database against a user-defined query.

Isolation and in silico evaluation of antidiabetic molecules of Cynodon dactylon (L.)

Hasthi V. Annapurna, Babu Apoorva, Natesan Ravichandran, Kallur Purushothaman Arun, Pemaiah Brindha, Sethuraman Swaminathan, Mahadevan Vijayalakshmi, Arumugam Nagarajan [PSG College of Pharmacy, Peelamedu]

J. Mol.Graph. and Mod., **39,** 87-97, 2013.

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Cynodon dactylon is a potential source of metabolites such as flavanoids, alkaloids, glycosides and β-sitosterol and has been traditionally employed to treat urinary tract and other microbial infections and dysentery. The present work attempts to evaluate the activity of C. dactylon extracts for glycemic control. Aqueous extracts of C. dactylon analyzed by HPLC–ESI MS have identified the presence of apigenin, luteolin, 6-C-pentosyl-8-C-hexosyl apigenin and 6-C-hexosyl-8-C-pentosyl luteolin.

Medicinal Chemistry and Drug Design (Cont'd)

Virtual screening for alpha7 nicotinic acetylcholine receptor for treatment of Alzheimer's disease

Shi-Gao Chen, Ruo-Xu Gu, Hao Dai, Dong-Qing Wei [Shanghai Jiao Tong University]

J. Mol.Graph. and Mod., **39,** 98-107, 2013.

Alzheimer's disease (AD) is the most common form of dementia. Although its cause and mechanism of progression are not well understood, various in vitro and in vivo experiments have proved that the decreased activity of the cholinergic neuron is responsible for the memory damage that is observed in these patients. Therefore, the nicotinic acetylcholine receptor (nAChR) is one of the possible drug targets for this disease. In the current study, we built homology models of α7 nAChR and virtually screened possible nAChR ligands by combining molecular docking, molecular feature searches, hydrogen bond analyses, and QSAR study.

Pharmacophore modeling and virtual screening studies to design potential COMT inhibitors as new leads

Nidhi Jatana, Aditya Sharma, N. Latha [Sri Venkateswara College (University of Delhi)]

J. Mol.Graph. and Mod., **39,** 145-164, 2013.

Catechol-O-methyltransferase (COMT) catalyzes the methylation of catecholamines, including neurotransmitters like dopamine, epinephrine and norepinephrine, leading to their degradation. COMT has been a subject of study for its implications in numerous neurological disorders like Parkinson's disease (PD), schizophrenia, and depression. The COMT gene is associated with many allelic variants, the Val108Met polymorphism being the most clinically significant. In this study, E-pharmacophore was also used to generate pharmacophore models based on a series of known COMT inhibitors.

Designing of new multi-targeted inhibitors of spleen tyrosine kinase (Syk) and zeta-associated protein of 70 kDa (ZAP-70) using hierarchical virtual screening protocol

Maninder Kaur, Archna Kumari, Malkeet Singh Bahia, Om Silakari [Punjabi University]

J. Mol.Graph. and Mod., **39,** 165-175, 2013.

In the present study, diverse inhibitor molecules of two protein tyrosine kinases i.e. Syk and ZAP-70 were considered for the pharmacophore and docking analyses to design new multi-targeted agents for these enzymes. These enzymes are non-receptor protein tyrosine kinases and both are expressed mainly in B and T-lymphocytes where they play a crucial role in immune signaling. The role of these two enzymes in inflammatory and autoimmune diseases makes them potential therapeutic targets for the designing of new multi-targeted agents to combat disease conditions associated with them.

In silico modeling of the type 2 IDI enzymes of Bacillus licheniformis, Pseudomonas stutzeri, Streptococcus pyogenes, and Staphylococcus aureus for virtual screening of potential inhibitors of this therapeutic target

Ibrahim Torktaz, Hossein Shahbani Zahiri [National Institute of Genetic Engineering and Biotechnology (NIGEB)], Kambiz Akbari Noghabi

J. Mol.Graph. and Mod., **39,** 176-182, 2013.

A!

Isopentenyl diphosphate isomerase is an essential enzyme in those living organisms such as pathogenic strains of Streptococcus and Staphylococcus genera which rely on the Mevalonate pathway for the production of isoprenoids. Therefore, the type 2 IDI may be a potential target for the therapy of some infectious diseases. In the current study, a virtual screening by docking was performed among 2000 chemicals from CoCoCo library to find a specific inhibitor for type 2 IDIs. To this end, the structures of the type 2 IDIs of Bacillus licheniformis, Pseudomonas stutzeri, Streptococcus pyogenes, and Staphylococcus aureus were molded using comparative modeling and Hidden Markov Model (HMM) based prediction.

Medicinal Chemistry and Drug Design (Cont'd)

Replica exchange molecular dynamics simulation of chitosan for drug delivery system based on carbon nanotube

Chompoonut Rungnim, Thanyada Rungrotmongkol, Supot Hannongbua [Institute for Molecular Science, Okazaki], Hisashi Okumura

J. Mol.Graph. and Mod., **39,** 183-192, 2013.

Chitosan is an important biopolymer in the medical applications because of its excellent biocompatibility. It has been recently highlighted in the targeted drug delivery system (DDS) by improvement of the carbon nanotube (CNT) solubility. To investigate the effect of chitosan length, the two targeted DDSs with 30 and 60 chitosan monomers were performed by replica-exchange molecular dynamics simulations at temperatures in the range of 300–455 K with three different combinations of force fields and implicit solvation models. Each DDS model contains the epidermal growth factor (EGF), chitosan (CS) of 30 (30CS) and 60 (60CS) monomers, single-wall CNT (SWCNT) and gemcitabine (Gemzar) as the model payload anticancer drug, called EGF/30CS/SWCNT/Gemzar and EGF/60CS/SWCNT/Gemzar, respectively.

Quantitative Structure-Activity Relations

Synthesis, pharmacological evaluation and QSAR modeling of mono-substituted 4-phenylpiperidines and 4-phenylpiperazines

Fredrik Pettersson [NeuroSearch Sweden AB], Peder Svensson, Susanna Waters, Nicholas Waters, Clas Sonesso

Europ. Jou. Med. Chem., **62**, 241-255, 2013.

A series of mono-substituted 4-phenylpiperidines and -piperazines have been synthesized and their effects on the dopaminergic system tested in vivo. The structure activity relationship (SAR) revealed that the position and physicochemical character of the aromatic substituent proved to be critical for the levels of 3,4-dihydroxyphenylacetic acid (DOPAC) in the brain of freely moving rats. In order to investigate how the structural properties of these compounds affect the response, a set of tabulated and calculated physicochemical descriptors were modeled against the in vivo effects using partial least square (PLS) regression.

Host-Guest Systems

On the Role of Dewetting Transitions in Host–Guest Binding Free Energy Calculations

Kathleen E. Rogers [University of California San Diego], Juan Manuel Ortiz-Sánchez, Riccardo Baron, Mikolai Fajer, César Augusto F. de Oliveira, and J. Andrew McCammon

J. Chem. Theor. and Comp, **9**, 46–53, 2013.

We use thermodynamic integration (TI) and explicit solvent molecular dynamics (MD) simulation to estimate the absolute free energy of host–guest binding. In the unbound state, water molecules visit all of the internally accessible volume of the host, which is fully hydrated on all sides. Upon binding of an apolar guest, the toroidal host cavity is fully dehydrated; thus, during the intermediate λ stages along the integration, the hydration of the host fluctuates between hydrated and dehydrated states.

Zeolites

Formation Pathway for LTA Zeolite Crystals Synthesized via a Charge Density Mismatch Approach

Min Bum Park, Yoorim Lee, Anmin Zheng, Feng-Shou Xiao, Christopher P. Nicholas, Gregory J. Lewis, and Suk Bong Hong [POSTECH]

J. Am. Chem. Soc., **135**, 2248–2255, 2013.

A solid understanding of the molecular-level mechanisms responsible for zeolite crystallization remains one of the most challenging issues in modern zeolite science. Here we investigated the formation pathway for high-silica LTA zeolite crystals in the simultaneous presence of tetraethylammonium (TEA^+), tetramethylammonium (TMA^+), and Na^+ ions as structure-directing agents (SDAs) with the goal of better understanding the charge density mismatch synthesis approach, which was designed to foster cooperation between two or more different SDAs.

Carbon Nanoparticles

Electric field effect on the zigzag (6,0) single-wall BC_2N nanotube for use in nano-electronic circuits

Mohammad T. Baei [Islamic Azad University], Ali Ahmadi Peyghan, Masoumeh Moghimi, Saeede Hashemian

J. Mol.Mod., **19,** 97-107, 2013.

We have analyzed the effect of external electric field on the zigzag (6,0) single-wall BC_2N nanotube using density functional theory calculations. Analysis of the structural parameters indicates that the nanotube is resistant against the external electric field strengths. Analysis of the electronic structure of the nanotube indicates that the applied parallel electric field strengths have a much stronger interaction with the nanotube with respect to the transverse electric field strengths and the nanotube is easier to modulate by the applied parallel electric field.

Density functional study on the adsorption of the drug isoniazid onto pristine and B-doped single wall carbon nanotubes

Nabanita Saikia, Ramesh C. Deka [Tezpur University]

J. Mol.Mod., **19,** 215-226, 2013.

The current study explores a new strategy to incorporate single wall carbon nanotubes (SWNTs)/doped SWNTs as carrier modules in target-specific administration of antitubercular chemotherapeutics through covalent and noncovalent functionalization onto the nanotube sidewall. Density functional studies illustrate that noncovalent functionalization of isoniazid (INH) is preferred over covalent attachment, exhibiting low adsorption energy values, HOMO–LUMO gap and comparison of quantum molecular descriptors performed in (5,5) and (9,0) SWNT systems.

Hydrogen dissociation on diene-functionalized carbon nanotubes

Javad Beheshtian, Ali Ahmadi Peyghan [Islamic Azad University], Zargham Bagheri

J. Mol.Mod., **19,** 255-261, 2013.

Chemical functionalization of a zigzag carbon nanotube (CNT) with 1, 3-cyclohexadiene (CHD), previously reported by experimentalists, has been investigated in the present study using density functional theory in terms of energetic, geometric, and electronic properties. Then, the thermodynamic and kinetic feasibility of H_2 dissociation on the pristine and functionalized CNTs have been compared. The dissociation energy of the H_2 molecule on the pristine and functionalized CNT has been calculated to be about −1.00 and −1.55 eV, while the barrier energy is found to be about 3.70 and 3.51 eV, respectively.

Carbon Nanoparticles (Cont'd)

Carbon nanotube functionalization with carboxylic derivatives: a DFT study

Javad Beheshtian, Ali Ahmadi Peyghan [Islamic Azad University], Zargham Bagheri

J. Mol.Mod., **19,** 391-396, 2013.

Chemical functionalization of a single-walled carbon nanotube (CNT) with different carboxylic derivatives including –COOX (X = H, CH_3, CH_2NH_2, CH_3Ph, CH_2NO_2, and CH_2CN) has been theoretically investigated in terms of geometric, energetic, and electronic properties. Reaction energies have been calculated to be in the range of −0.23 to −7.07 eV. The results reveal that the reaction energy is increased by increasing the electron withdrawing character of the functional groups so that the relative magnitude order is $-CH_2NO_2 > -CH_2CN > -H > -CH_2Ph > -CH_3 > -CH_2NH_2$.

A DFT study on the initial stage of thermal degradation of Poly(methyl methacrylate)/carbon nanotube system

Benoit Minisini [ISMANS, 44 Avenue F A Bartholdi], Emerson Vathonne, Carine Chivas-Joly

J. Mol.Mod., **19,** 623-629, 2013.

A!

DFT calculations, with VWN exchange correlation functional and double numeric basis set, were used to evaluate the energies required for the scission reactions taking place in the initial stage of the thermal degradation of Poly(methyl methacrylate) (PMMA) in the presence of a carbon nanotube (CNT). Side group and main chain scissions were investigated. The results averaged from five configurations of pure PMMA (DP = 5) were used as references and compared to the results obtained for the five same configurations of PMMA grafted on three carbon nanotubes of similar diameter (1.49 nm).

$BaTiO_3$-based nanolayers and nanotubes: First-principles calculations

Robert A. Evarestov [St. Petersburg State University], Andrei V. Bandura and Dmitrii D. Kuruch

J. Comp. Chem., **34**, 175–186, 2013.

The first-principles calculations using hybrid exchange-correlation functional and localized atomic basis set are performed for $BaTiO_3$ (BTO) nanolayers and nanotubes (NTs) with the structure optimization. Both the cubic and the ferroelectric BTO phases are used for the nanolayers and NTs modeling. It follows from the calculations that nanolayers of the different ferroelectric BTO phases have the practically identical surface energies and are more stable than nanolayers of the cubic phase.

Interparticle Dispersion, Membrane Curvature, and Penetration Induced by Single-Walled Carbon Nanotubes Wrapped with Lipids and PEGylated Lipids

Hwankyu Lee [Dankook University, Yongin]

J. Phys. Chem. B., **117**, 1337–1344, 2013**.**

Single-walled carbon nanotubes (SWNTs) wrapped with different types of lipids and polyethylene glycol (PEG)-grafted lipids were simulated with lipid bilayers. Simulations were carried out with the previously parametrized coarse-grained (CG) SWNT and PEG force fields that had captured the experimentally observed conformations of self-assembled SWNT–lipid complexes and phase behavior of PEG-grafted lipids. Simulations of multiple copies of the SWNT in water show that all pure SWNTs aggregate, lipid-wrapped SWNTs partially aggregate, but those wrapped with lipids grafted to PEG (M_w = 550) completely disperse, indicating the effect of short PEG chains on interparticle aggregation, in agreement with experiment.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

PLI: a web-based tool for the comparison of protein-ligand interactions observed on PDB structures

Anna Maria Gallina, Paola Bisignano, Maurizio Bergamino, and Domenico Bordo [IST—Istituto Nazionale Ricerca sul Cancro]

Bioinformatics. **29**, 395-397, 2013.

A large fraction of the entries contained in the Protein Data Bank describe proteins in complex with low molecular weight molecules such as physiological compounds or synthetic drugs. The web service protein-ligand interaction presented here provides a tool to analyse and compare the binding pockets of homologous proteins in complex with a selected ligand. The information is deduced from protein-ligand complexes present in the Protein Data Bank and stored in the underlying database.

Characterization of disordered proteins with ENSEMBLE

Mickaël Krzeminski, Joseph A. Marsh, Chris Neale, Wing-Yiu Choy, and Julie D. Forman-Kay [Hospital for Sick Children, Toronto]

Bioinformatics. **29**, 398-399, 2013.

ENSEMBLE is a computational approach for determining a set of conformations that represents the structural ensemble of a disordered protein based on input experimental data. The disordered protein can be an unfolded or intrinsically disordered state. Here, we introduce the latest version of the program, which has been enhanced to facilitate its general release and includes an intuitive user interface, as well as new approaches to treat data and analyse results.

S4MPLE – Sampler For Multiple Protein–Ligand Entities: Simultaneous Docking of Several Entities

Laurent Hoffer and Dragos Horvath [Université de Strasbourg]

J.Chem. Infor. and Mod. **53**, 88–102, 2013.

S4MPLE is a conformational sampling tool, based on a hybrid genetic algorithm, simulating one (conformer enumeration) or more molecules (docking). Energy calculations are based on the AMBER force field [Cornell et al. J. Am. Chem. Soc. 1995, 117, 5179.] for biological macromolecules and its generalized version GAFF [Wang et al. J. Comput. Chem. 2004, 25, 1157.] for ligands. This paper describes more advanced, specific applications of S4MPLE to problems more complex than classical redocking of drug-like compounds [Hoffer et al. J. Mol. Graphics Modell. 2012, submitted for publication.].

An Automated Docking Protocol for hERG Channel Blockers

Giovanni Paolo Di Martino, Matteo Masetti [Alma Mater Studiorum], Luisa Ceccarini, Andrea Cavalli, and Maurizio Recanatini

J.Chem. Infor. and Mod. **53**, 159–175, 2013.

A docking protocol aimed at obtaining a consistent qualitative and quantitative picture of binding for a series of hERG channel blockers is presented. To overcome the limitations experienced by standard procedures when docking blockers at hERG binding site, we designed a strategy that explicitly takes into account the conformations of the channel, their possible intrinsic symmetry, and the role played by the configurational entropy of ligands. The protocol was developed on a series of congeneric sertindole derivatives, allowing us to satisfactorily explain the structure–activity relationships for this set of blockers.

Bioinformatics and Cheminformatics (Cont'd)

OpenMM 4: A Reusable, Extensible, Hardware Independent Library for High Performance Molecular Simulation

Peter Eastman [Stanford University], Mark S. Friedrichs, John D. Chodera, Randall J. Radmer, Christopher M. Bruns, Joy P. Ku, Kyle A. Beauchamp, Thomas J. Lane, Lee-Ping Wang, Diwakar Shukla, Tony Tye, Mike Houston, Timo Stich, Christoph Klein, Michael R. Shirts, and Vijay S. Pande

J. Chem. Theor. and Comp, **9**, 461–469, 2013.

OpenMM is a software toolkit for performing molecular simulations on a range of high performance computing architectures. It is based on a layered architecture: the lower layers function as a reusable library that can be invoked by any application, while the upper layers form a complete environment for running molecular simulations. The library API hides all hardware-specific dependencies and optimizations from the users and developers of simulation programs: they can be run without modification on any hardware on which the API has been implemented. The current implementations of OpenMM include support for graphics processing units using the OpenCL and CUDA frameworks.

EuLoc: a web-server for accurately predict protein subcellular localization in eukaryotes by incorporating various features of sequence segments into the general form of Chou's PseAAC

Tzu-Hao Chang [Taipei Medical University], Li-Ching Wu, Tzong-Yi Lee, Shu-Pin Chen, Hsien-Da Huang, Jorng-Tzong Horng

J. Comp. Aided Mol. Des.,**27**, 91-103, 2013.

The function of a protein is generally related to its subcellular localization. Therefore, knowing its subcellular localization is helpful in understanding its potential functions and roles in biological processes. This work develops a hybrid method for computationally predicting the subcellular localization of eukaryotic protein. The method is called EuLoc and incorporates the Hidden Markov Model (HMM) method, homology search approach and the support vector machines (SVM) method by fusing several new features into Chou's pseudo-amino acid composition. The proposed SVM module overcomes the shortcoming of the homology search approach in predicting the subcellular localization of a protein which only finds low-homologous or non-homologous sequences in a protein subcellular localization annotated database.

Lattice microbes: High-performance stochastic simulation method for the reaction-diffusion master equation

Elijah Roberts, John E. Stone and Zaida Luthey-Schulten [University of Illinois at Urbana-Champaign]

J. Comp. Chem., **34**, 245–255, 2013.

Spatial stochastic simulation is a valuable technique for studying reactions in biological systems. With the availability of high-performance computing (HPC), the method is poised to allow integration of data from structural, single-molecule and biochemical studies into coherent computational models of cells. Here, we introduce the Lattice Microbes software package for simulating such cell models on HPC systems. The software performs either well-stirred or spatially resolved stochastic simulations with approximated cytoplasmic crowding in a fast and efficient manner.

Protein Secondary Structure

The Role of the Flexible L43-S54 Protein Loop in the CcrA Metallo-β-lactamase in Binding Structurally Dissimilar β-Lactam Antibiotics

Crystal E. Valdez, Manuel Sparta, and Anastassia N. Alexandrova [University of California, Los Angeles]

J. Chem. Theor. and Comp, **9**, 730–737, 2013.

The CcrA di-Zn β-lactamase is a bacterial enzyme capable of efficiently hydrolyzing and thus disabling a diverse set of β-lactam antibiotics. Understanding the factors that contribute to the efficiency of CcrA is essential for the design of new CcrA-resistant antibiotics and enzyme inhibitors. The efficacy of CcrA has been speculated to be partially attributable to the flexible protein loop located above the active site (L43-S54), which would mold around structurally different substrates, for snag binding.

Comparative or Homology Modeling

Homology modeling and docking studies of FabH (β-ketoacyl-ACP synthase III) enzyme involved in type II fatty acid biosynthesis of Chlorella variabilis: a potential algal feedstock for biofuel production

Namrata Misra, Mahesh Chandra Patra, Prasanna Kumar Panda, Lala Bihari Sukla & Barada Kanta Mishra [CSIR-Institute of Minerals and Materials Technology]

J. Biomol. Stru. and Dyn., **31**, 241-257, 2013.

A!

The concept of using microalgae as an alternative renewable source of biofuel has gained much importance in recent years. Unraveling the fatty acid metabolic pathway and understanding structural features of various key enzymes regulating the process will provide valuable insights to target microalgae for augmented oil content. FabH (β-ketoacyl-acyl carrier protein synthase; KAS III) is a condensing enzyme catalyzing the initial elongation step of type II fatty acid biosynthetic process and acyl carrier protein (ACP) facilitates the shuttling of the fatty acyl intermediates to the active site of the respective enzymes in the pathway. In the present study, a reliable three-dimensional structure of FabH from Chlorella variabilis, an oleaginous green microalga was modeled and subsequently the key residues involved in substrate binding were determined by employing protein–protein docking and MD simulation protocols.

Simulation of homology models for the extracellular domains (ECD) of ErbB3, ErbB4 and the ErbB2–ErbB3 complex in their active conformations

Juan Felipe Franco-Gonzalez, Javier Ramos, Victor L. Cruz [Instituto de Estructura de la Materia], Javier Martínez-Salazar

J. Mol.Mod., **19,** 931-941, 2013.

Epidermal growth factor receptors (EGFR) are associated with a number of biological processes and are becoming increasingly recognized as important therapeutic targets against cancer. In this work, we provide models based on homology for the extracellular domains (ECD) of ErbB3 and ErbB4 in their active conformations, including a Heregulin ligand, followed by further refinement of the models by molecular dynamics simulations at atomistic scale.

Comparative or Homology Modeling (Cont'd)

Docking and MD study of histamine H4R based on the crystal structure of H1R

Zhiwei Feng, Tingjun Hou, Youyong Li [Soochow University]

J. Mol.Graph. and Mod., **39,** 1-12, 2013.

Histamine H4 receptor (H4R), a member of histamine receptor family, which belongs to class A of G-protein coupled receptors (GPCRs), has been reported to play a critical role in histamine-induced chemotaxis in mast cells and eosinophils. Recently, the crystal structure of human histamine H1 receptor (H1R) was reported, which facilitates structure-based drug discovery of histamine receptor significantly. In the current work, the homology models of H4R and H3R are first constructed based on the crystal structure of H1R. Clobenpropit is then docked into the binding pocket of H4R and two different binding modes can be identified.

A homology modeling study toward the understanding of three-dimensional structure and putative pharmacological profile of the G-protein coupled receptor GPR55

Orgil Elbegdorj, Richard B. Westkaemper, Yan Zhang [Virginia Commonwealth University]

J. Mol.Graph. and Mod., **39,** 50-60, 2013.

A!

The orphan G-protein coupled receptor GPR55 was shown to bind to certain cannabinoid compounds which led to its initial classification as the third type of cannabinoid receptor. Later studies showed that lysophosphatidylinositol (LPI) also activated GPR55, in particular 2-arachidonoyl-LPI was proposed to be its endogenous ligand. Herein, we report the ligand binding properties of GPR55 by applying homology modeling and automated docking algorithms in order to understand its pharmacological profile.

Homology modeling and virtual screening approaches to identify potent inhibitors of slingshot phosphatase 1

Hwangseo Park [Sejong University], So Ya Park, Seong Eon Ryu

J. Mol.Graph. and Mod., **39,** 65-70, 2013.

A!

Although slingshot phosphatase 1 (SSH1) proved to be a promising target for the development of therapeutics for the treatment of vascular diseases and cancers, no small-molecule inhibitor has been reported so far. We have been able to identify eight novel inhibitors of SSH1 through the computer-aided drug design protocol involving homology modeling of SSH1 structure, virtual screening of a large chemical library with docking simulations, and in vitro enzyme assays. The identified inhibitors revealed high potencies with the associated IC_{50} values ranging from 2.8 to 12.7 μM and were also screened for having desirable physicochemical properties as a drug candidate.

A structural and functional model for human bone sialoprotein

Kevin Vincent, Marcus C. Durrant [Northumbria University]

J. Mol.Graph. and Mod., **39,** 108-117, 2013.

A!

Human bone sialoprotein (BSP) is an essential component of the extracellular matrix of bone. It is thought to be the primary nucleator of hydroxyapatite crystallization, and is known to bind to hydroxyapatite, collagen, and cells. Mature BSP shows extensive post-translational modifications, including attachment of glycans, sulfation, and phosphorylation, and is highly flexible with no specific 2D or 3D structure in solution or the solid state. We have therefore developed a 3D structural model for BSP, based on the available literature data, using molecular modelling techniques.

Comparative or Homology Modeling (Cont'd)

Structural model of the Y-Family DNA polymerase V/RecA mutasome

Sushil Chandani, Edward L. Loechler [Boston University]

J. Mol.Graph. and Mod., **39,** 133-144, 2013.

To synthesize past DNA damaged by chemicals or radiation, cells have lesion bypass DNA polymerases (DNAPs), most of which are in the Y-Family. One class of Y-Family DNAPs includes DNAP η in eukaryotes and DNAP V in bacteria, which have low fidelity when replicating undamaged DNA. Taking a docking approach, ~150,000 unique orientations involving UmuC, UmuD' and RecA were evaluated to generate models, one of which was judged best able to rationalize many published findings.

Prediction of protein domain boundaries from inverse covariances

Michael I. Sadowski [MRC National Institute for Medical Research]

Proteins: Stru. Fun. & Bioinf., **81**, 253–260, 2013.

It has been known even since relatively few structures had been solved that longer protein chains often contain multiple domains, which may fold separately and play the role of reusable functional modules found in many contexts. In many structural biology tasks, in particular structure prediction, it is of great use to be able to identify domains within the structure and analyze these regions separately. We test several methods for using this information including a kernel smoothing-based approach and methods based on building alpha-carbon models and compare performance with a length-based predictor, a homology search method and four published sequence-based predictors: DOMCUT, DomPRO, DLP-SVM, and SCOOBY-DOmain.

Protein Confirmational Analysis

Computational study of EGFR inhibition: molecular dynamics studies on the active and inactive protein conformations

Napat Songtawee, M. Paul Gleeson, Kiattawee Choowongkomon [Kasetsart University]

J. Mol.Mod., **19,** 497-509, 2013.

The structural diversity observed across protein kinases, resulting in subtly different active site cavities, is highly desirable in the pursuit of selective inhibitors, yet it can also be a hindrance from a structure-based design perspective. An important challenge in structure-based design is to better understand the dynamic nature of protein kinases and the underlying reasons for specific conformational preferences in the presence of different inhibitors. To investigate this issue, we performed molecular dynamics simulation on both the active and inactive wild type epidermal growth factor receptor (EGFR) protein with both type-I and type-II inhibitors.

A!

Protein Confirmational Analysis (Cont'd)

Engineering strategy to improve peptide analogs: from structure-based computational design to tumor homing

David Zanuy [Universitat Politècnica de Catalunya], Francisco J. Sayago, Guillem Revilla-López, Gema Ballano, Lilach Agemy, Venkata Ramana Kotamraju, Ana I. Jiménez, Carlos Cativiela, Ruth Nussinov, April M. Sawvel, Galen Stucky, Erkki Ruoslahti, Carlos Alemán

J. Comp. Aided Mol. Des.,**27**, 31-43, 2013.

We present a chemical strategy to engineer analogs of the tumor-homing peptide CREKA (Cys-Arg-Glu-Lys-Ala), which binds to fibrin and fibrin-associated clotted plasma proteins in tumor vessels (Simberg et al. in Proc Natl Acad Sci USA 104:932–936, 2007) with improved ability to inhibit tumor growth. Computer modeling using a combination of simulated annealing and molecular dynamics were carried out to design targeted replacements aimed at enhancing the stability of the bioactive conformation of CREKA. Because this conformation presents a pocket-like shape with the charged groups of Arg, Glu and Lys pointing outward, non-proteinogenic amino acids α-methyl and N-methyl derivatives of Arg, Glu and Lys were selected, rationally designed and incorporated into CREKA analogs.

Relationship between Conformational Dynamics and Electron Transfer in a Desolvated Peptide. Part I. Structures

David Semrouni, Carine Clavaguéra, and Gilles Ohanessian [Ecole Polytechnique], Joel H. Parks

J. Phys. Chem. B., **117**, 1746–1755, 2013**.**

The structures, dynamics and energetics of the protonated, derivatized peptide DyeX-$(Pro)_4$-Arg^+-Trp, where "Dye" stands for the BODIPY analogue of tetramethylrhodamine and X is a $(CH_2)_5$ linker, have been investigated using a combination of modeling approaches in order to provide a numerical framework to the interpretation of fluorescence quenching data in the gas phase. Molecular dynamics (MD) calculations using the new generation AMOEBA force field were carried out using a representative set of conformations, at eight temperatures ranging from 150 to 500 K. Force field parameters were derived from ab initio calculations for the Dye.

Protein Structure Analysis

Molecular dynamics simulations reveal structural instability of human trypsin inhibitor upon D50E and Y54H mutations

Wanwimon Mokmak, Surasak Chunsrivirot, Anunchai Assawamakin, Kiattawee Choowongkomon, Sissades Tongsima [National Center for Genetic Engineering and Biotechnology, 113 Thailand Science Park]

J. Mol.Mod., **19,** 521-528, 2013.

Serine protease inhibitor Kazal type 1 (SPINK1) plays an important role in protecting the pancreas against premature trypsinogen activation that causes pancreatitis. Various mutations in the SPINK1 gene were shown to be associated with patients with pancreatitis. Recent transfection studies identified intracellular folding defects, probably caused by mutation induced misfolding of D50E and Y54H mutations, as a common mechanism that reduces SPINK1 secretion and as a possible novel mechanism of SPINK1 deficiency associated with chronic pancreatitis. Using molecular dynamics, we investigated the effects of D50E and Y54H mutations on SPINK1 dynamics and conformation at 300 K.

Protein Dynamics

The Backbone Dynamics of the Amyloid Precursor Protein Transmembrane Helix Provides a Rationale for the Sequential Cleavage Mechanism of γ-Secretase

Oxana Pester, Paul J. Barrett, Daniel Hornburg, Philipp Hornburg, Rasmus Pröbstle, Simon Widmaier, Christoph Kutzner, Milena Dürrbaum, Aphrodite Kapurniotu, Charles R. Sanders, Christina Scharnagl, and Dieter Langosch [Technische Universität München]

J. Am. Chem. Soc., **135**, 1317–1329, 2013.

The etiology of Alzheimer's disease depends on the relative abundance of different amyloid-β (Aβ) peptide species. These peptides are produced by sequential proteolytic cleavage within the transmembrane helix of the 99 residue C-terminal fragment of the amyloid precursor protein (C99) by the intramembrane protease γ-secretase. Intramembrane proteolysis is thought to require local unfolding of the substrate helix, which has been proposed to be cleaved as a homodimer. Here, we investigated the backbone dynamics of the substrate helix. Amide exchange experiments of monomeric recombinant C99 and of synthetic transmembrane domain peptides reveal that the N-terminal Gly-rich homodimerization domain exchanges much faster than the C-terminal cleavage region.

Interplay between Drying and Stability of a TIM Barrel Protein: A Combined Simulation–Experimental Study

Payel Das, Divya Kapoor, Kevin T. Halloran, Ruhong Zhou, and C. Robert Matthews [University of Massachusetts Medical School]

J. Am. Chem. Soc., **135**, 1882–1890, 2013.

A!

Recent molecular dynamics simulations have suggested important roles for nanoscale dewetting in the stability, function, and folding dynamics of proteins. Using a synergistic simulation–experimental approach on the αTS TIM barrel protein, we validated this hypothesis by revealing the occurrence of drying inside hydrophobic amino acid clusters and its manifestation in experimental measures of protein stability and structure. Cavities created within three clusters of branched aliphatic amino acids [isoleucine, leucine, and valine (ILV) clusters] were found to experience strong water density fluctuations or intermittent dewetting transitions in simulations.

Sequence Effects on Peptide Assembly Characteristics Observed by Using Scanning Tunneling Microscopy

Xiaobo Mao, Yuanyuan Guo, Yin Luo, Lin Niu, Lei Liu, Xiaojing Ma, Huibin Wang, Yanlian Yang, Guanghong Wei, and Chen Wang [National Center for Nanoscience and Technology]

J. Am. Chem. Soc., **135**, 2181–2187, 2013.

Homogeneous assemblies of the model peptides at interfaces have been achieved and observed with scanning tunneling microscopy. The dependence of the observed brightness in STM images is analyzed, and the correlation with the peptide residues is proposed. We have also investigated the conformational dynamics of the peptide assemblies adsorbed on a graphene sheet by performing all-atom molecular dynamic simulations in water at 300 K. The simulation results of the two peptide assemblies on graphite surfaces show that $R_4G_4H_8$ and $F_4G_4H_8$ peptide assemblies are mostly in β-sheet structure, and the interaction energy of the four different residues with graphite surfaces follows the order of Phe > His > Arg > Gly, consistent with their brightness contrasts in STM images.

Protein Dynamics (Cont'd)

Molecular dynamics simulations and density functional theory studies of NALMA and NAGMA dipeptides

Subramaniam Boopathi & Ponmalai Kolandaivel [Bharathiar University]

J. Biomol. Stru. and Dyn., **31**, 158-173, 2013.

A!

Classical molecular dynamics (MD) simulations using fixed charged force field (AMBER ff03) and density functional theory method using the M05-2X/6-31G** level of theory have been used to investigate the plasticity of the hydrogen bond formed between dipeptides of N-Acetyl-Leucine-MethylAmide (NALMA), N-Acetyl-Glycine-MethylAmide (NAGMA), and vicinity of water molecules at temperature of 300 K. We have noticed that 2–3 water molecules contribute to change in the conformations of dipeptides NAGMA and NALMA.

Comparative simulation studies of native and single-site mutant human beta-defensin-1 peptides

Rabab A. Toubar, Artem Zhmurov, Valeri Barsegov & Kenneth A. Marx [University of Massachusetts Lowell]

J. Biomol. Stru. and Dyn., **31**, 174-194, 2013.

A!

Human defensins play important roles in a broad range of biological functions, such as microbial defense and immunity. Yet, little is known about their molecular properties, i.e. secondary structure stability, structural variability, important side chain interactions, surface charge distribution, and resistance to thermal fluctuations, and how these properties are related to their functions. To assess these factors, we studied the native human β-defensin-1 monomer and dimer as well as several single-site mutants using molecular dynamics simulations. The results showed that disulfide bonds are important determinants in maintaining the defensins' structural integrity, as no structural transitions were observed at 300 K and only minor structural unfolding was detected upon heating to 500 K.

Enhanced sampling of molecular dynamics simulation of peptides and proteins by double coupling to thermal bath

Changjun Chen, Yanzhao Huang & Yi Xiao [Huazhong University of Science and Technology]

J. Biomol. Stru. and Dyn., **31**, 206-214, 2013.

Low sampling efficiency in conformational space is the well-known problem for conventional molecular dynamics. It greatly increases the difficulty for molecules to find the transition path to native state, and costs amount of CPU time. To accelerate the sampling, in this paper, we re-couple the critical degrees of freedom in the molecule to environment temperature, like dihedrals in generalized coordinates or nonhydrogen atoms in Cartesian coordinate. After applying to ALA dipeptide model, we find that this modified molecular dynamics greatly enhances the sampling behavior in the conformational space and provides more information about the state-to-state transition, while conventional molecular dynamics fails to do so.

Protein Dynamics (Cont'd)

In silico structural and functional analysis of the human TOPK protein by structure modeling and molecular dynamics studies

Palani Kirubakaran, Muthusamy Karthikeyan [Alagappa University], Kh. Dhanachandra Singh, Selvaraman Nagamani, Kumpati Premkumar

J. Mol.Mod., **19,** 407-419, 2013.

A!

Over expression of T-lymphokine–activated killer cell–originated protein kinase (TOPK) has been associated with leukemia, myeloma tumors and various other cancers. The function and regulatory mechanism of TOPK in tumor cells remains unclear. Structural studies that could reveal the regulatory mechanism have been a challenge because of the unavailabity of TOPK's crystal structure. Hence, in this study, the 3D structure of TOPK protein has been constructed by using multiple templates. The quality and reliability of the generated model was checked and the molecular dynamics method was utilized to refine the model.

Cyclo-hexa-peptides at the water/cyclohexane interface: a molecular dynamics simulation

Min Cen, Jian Fen Fan [Soochow University, Suzhou], Dong Yan Liu, Xue Zeng Song, Jian Liu, Wei Qun Zhou, He Ming Xiao

J. Mol.Mod., **19,** 601-611, 2013.

A!

Molecular dynamic (MD) simulations have been performed to study the behaviors of ten kinds of cyclo-hexa-peptides (CHPs) composed of amino acids with the diverse hydrophilic/hydrophobic side chains at the water/cyclohexane interface. All the CHPs take the "horse-saddle" conformations at the interface and the hydrophilicity/hydrophobicity of the side chains influences the backbones' structural deformations. The orientations and distributions of the CHPs at the interface and the differences of interaction energies ($\Delta\Delta E$) between the CHPs and the two liquid phases have been determined.

Computational investigation of the key factors affecting the second stage activation mechanisms of domain II m-calpain

Gaurav Bhatti, Lakshmi Jayanthi, Pamela VandeVord, Yeshitila Gebremichael [Wayne State University]

J. Mol.Mod., **19,** 779-792, 2013.

A!

The unique conformation of the active site in calpains along with the implication of their role in several diseases has prompted widespread research interest in the scientific community. Structural studies devoted to m- and μ-calpains have proposed a two-stage calcium-dependent activation mechanism for calpains. In this work, we performed conventional and targeted molecular dynamics simulations to investigate global and local changes in the structure of the protease core of m-calpain upon calcium binding.

Steered molecular dynamics simulation of the binding of the β2 and β3 regions in domain-swapped human cystatin C dimer

Jianwei He, Linan Xu, Shuo Zhang, Jing Guan, Manli Shen, Hui Li, Youtao Song [Liaoning University]

J. Mol.Mod., **19,** 825-832, 2013.

The crystal structure of the human cystatin C (hCC) dimer revealed that a stable twofold-symmetric dimer was formed via 3D domain swapping. Domain swapping with the need for near-complete unfolding has been proposed as a possible route for amyloid fibril initiation. Thus, the interesting interactions that occur between the two molecules may be important for the further aggregation of the protein. In this work, we performed steered molecular dynamics (SMD) simulations to investigate the dissociation of the β2 and β3 strands in the hCC dimer.

Protein Dynamics (Cont'd)

Adsorption of amino acids on the magnetite-(111)-surface: a force field study

Andreas Bürger [Ruhr-Universität Bochum], Uta Magdans, Hermann Gies

J. Mol.Mod., **19,** 851-857, 2013.

A!

Magnetite (Fe_3O_4) is an important biomineral, e.g., used by magnetotactic bacteria. The connection between the inorganic magnetite-(111)-surface and the organic parts of the bacteria is the magnetosome membrane. The membrane is built by different magnetosome membrane proteins (MMPs), which are dominated by the four amino acids glycine (Gly), aspartic acid (Asp), leucine (Leu) and glutamic acid (Glu). Force field simulations of the interaction of the magnetite-(111)-surface and the main amino acid compounds offer the possibility to investigate if and how the membrane proteins could interact with the mineral surface thus providing an atomistic view on the respective binding sites.

Exploring the Molecular Mechanism of Cross-Resistance to HIV-1 Integrase Strand Transfer Inhibitors by Molecular Dynamics Simulation and Residue Interaction Network Analysis

Weiwei Xue, Xiaojie Jin, Lulu Ning, Meixia Wang, Huanxiang Liu, and Xiaojun Yao [Lanzhou University]

J.Chem. Infor. and Mod. **53**, 210–222, 2013.

The rapid emergence of cross-resistance to the integrase strand transfer inhibitors (INSTIs) has become a serious problem in the therapy of human immunodeficiency virus type 1 (HIV-1) infection. Understanding the detailed molecular mechanism of INSTIs cross-resistance is therefore critical for the development of new effective therapy against cross-resistance. On the basis of the homology modeling constructed structure of tetrameric HIV-1 intasome, the detailed molecular mechanism of the cross-resistance mutation E138K/Q148K to three important INSTIs (Raltegravir (RAL, FDA approved in 2007), Elvitegravir (EVG, FDA approved in 2012), and Dolutegravir (DTG, phase III clinical trials)) was investigated by using molecular dynamics (MD) simulation and residue interaction network (RIN) analysis.

Consistent View of Protein Fluctuations from All-Atom Molecular Dynamics and Coarse-Grained Dynamics with Knowledge-Based Force-Field

Michal Jamroz, Modesto Orozco, Andrzej Kolinski, and Sebastian Kmiecik [University of Warsaw]

J. Chem. Theor. and Comp, **9**, 119–125, 2013.

It is widely recognized that atomistic Molecular Dynamics (MD), a classical simulation method, captures the essential physics of protein dynamics. That idea is supported by a theoretical study showing that various MD force-fields provide a consensus picture of protein fluctuations in aqueous solution [Rueda, M. et al. Proc. Natl. Acad. Sci. U.S.A. **2007**, 104, 796–801]. However, atomistic MD cannot be applied to most biologically relevant processes due to its limitation to relatively short time scales. We demonstrate that the aforementioned consensus view of protein dynamics from short (nanosecond) time scale MD simulations is fairly consistent with the dynamics of the coarse-grained protein model - the CABS model.

Protein Dynamics (Cont'd)

PaLaCe: A Coarse-Grain Protein Model for Studying Mechanical Properties

Marco Pasi, Richard Lavery [Univ. Lyon I/CNRS UMR 5086, IBCP], and Nicoletta Ceres

J. Chem. Theor. and Comp, **9**, 785–793, 2013.

We present a coarse-grain protein model PaLaCe (Pasi–Lavery–Ceres) that has been developed principally to allow fast computational studies of protein mechanics and to clarify the links between mechanics and function. PaLaCe uses a two-tier protein representation with one to three pseudoatoms representing each amino acid for the main nonbonded interactions, combined with atomic-scale peptide groups and some side chain atoms to allow the explicit representation of backbone hydrogen bonds and to simplify the treatment of bonded interactions.

Implicit Solvent Models and Stabilizing Effects of Mutations and Ligands on the Unfolding of the Amyloid β-Peptide Central Helix

Alok Juneja, Mika Ito, and Lennart Nilsson [Karolinska Institutet,]

J. Chem. Theor. and Comp, **9**, 834–846, 2013.

We have systematically evaluated the ability of molecular dynamics simulation with implicit solvation models (EEF1.1, SASA, ASPENR, SCPISM, RUSH, ACE2, GBORN, GBSW, GBMV II, FACTS) to characterize the unfolding of the amyloid beta (Aβ) peptide and the stabilizing effects of mutations and ligands. The 13–26 region of Aβ ($A\beta_{13–26}$) unfolds and leads to the formation of amyloid fibrils, the causative agent of Alzheimer's disease. Stabilization of $A\beta_{13–26}$ decreases Aβ polymerization as well as the formation of intermediate structures, which may also be toxic.

A!

Rotamer decomposition and protein dynamics: Efficiently analyzing dihedral populations from molecular dynamics

Hiroshi Watanabe, Marcus Elstner and Thomas Steinbrecher [Inst. Phys. Chem.]

J. Comp. Chem., **34**, 198–205, 2013.

Molecular mechanics methods have matured into powerful methods to understand the dynamics and flexibility of macromolecules and especially proteins. As multinanosecond to microsecond length molecular dynamics (MD) simulations become commonplace, advanced analysis tools are required to generate scientifically useful information from large amounts of data. Some of the key degrees of freedom to understand protein flexibility and dynamics are the amino acid residue side chain dihedral angles. In this work, we present an easily automated way to summarize and understand the relevant dihedral populations.

Parameterization of the proline analogue Aze (azetidine-2-carboxylic acid) for molecular dynamics simulations and evaluation of its effect on homo-pentapeptide conformations

Kyrylo Bessonov, Kenrick A. Vassall, George Harauz [University of Guelph]

J. Mol.Graph. and Mod., **39,** 118-125, 2013.

We have parameterized and evaluated the proline homologue Aze (azetidine-2-carboxylic acid) for the gromos56a3 force-field for use in molecular dynamics simulations using GROMACS. Using bi-phasic cyclohexane/water simulation systems and homo-pentapeptides, we measured the Aze solute interaction potential energies, ability to hydrogen bond with water, and overall compaction, for comparison to Pro, Gly, and Lys. Compared to Pro, Aze has a slightly higher H-bonding potential, and stronger electrostatic but weaker non-electrostatic interactions with water.

Protein Dynamics (Cont'd)

Coarse-Grained Modeling of Protein Second Osmotic Virial Coefficients: Sterics and Short-Ranged Attractions

Alexander Grünberger, Pin-Kuang Lai, Marco A. Blanco, and Christopher J. Roberts [University of Delaware, Newark]

J. Phys. Chem. B., **117**, 763–770, 2013**.**

A series of coarse-grained models, with different levels of structural resolution, were tested to calculate the steric contributions to protein osmotic second virial coefficients ($B_{22,S}$) for proteins ranging from small single-domain molecules to large multidomain molecules, using the recently developed Mayer sampling method. $B_{22,S}$ was compared for different levels of coarse-graining: four-beads-per-amino-acid (4bAA), one-bead-per-amino-acid (1bAA), one-sphere-per-domain (1sD), and one-sphere-per-protein (1sP).

Site Specificity on OH α-H Abstraction Reaction for a Zwitterionic β-Hairpin Peptide in Aqueous Solution: A Theoretical Investigation

Ren-Jie Lin, Soonmin Jang, Hyunsik Kim, Chen-Chang Wu, and Feng-Yin Li [National Chung Hsing University]

J. Phys. Chem. B., **117**, 771–783, 2013**.**

Protein backbone oxidation was investigated by studying the α-H abstraction reaction in a ß-hairpin peptide, called Chignolin (PDB ID 1UAO), with density functional theory calculation at B3LYP/6-31G(d,p) without any constraint. In order to stabilize the zwitterionic form of Chignolin with the salt bridges, the effects of aqueous solution were implemented by using microsolvation combined with a conductor-like polarizable continuum model (CPCM). Comparison between three glycine residues located at three different sites in Chignolin was used to examine the possible site specificity of this backbone oxidation.

The Role of Amino Acid Sequence in the Self-Association of Therapeutic Monoclonal Antibodies: Insights from Coarse-Grained Modeling

Anuj Chaudhri, Isidro E. Zarraga, Sandeep Yadav, Thomas W. Patapoff, Steven J. Shire, and Gregory A. Voth [University of Chicago]

J. Phys. Chem. B., **117**, 1269–1279, 2013**.**

Coarse-grained computational models of therapeutic monoclonal antibodies and their mutants can be used to understand the effect of domain-level charge–charge electrostatics on the self-association phenomena at high protein concentrations. The coarse-grained models are constructed for two antibodies at different coarse-grained resolutions by using six different concentrations. It is observed that a particular monoclonal antibody (hereafter referred to as MAb1) forms three-dimensional heterogeneous structures with dense regions or clusters compared to a different monoclonal antibody (hereafter referred to as MAb2) that forms homogeneous structures without clusters.

Assessment of the Use of NMR Chemical Shifts as Replica-Averaged Structural Restraints in Molecular Dynamics Simulations to Characterize the Dynamics of Proteins

Carlo Camilloni, Andrea Cavalli, and Michele Vendruscolo [University of Cambridge, Lensfield Road]

J. Phys. Chem. B., **117**, 1838–1843, 2013**.**

It has been recently proposed that NMR chemical shifts can be used as replica-averaged structural restraints in molecular dynamics simulations to determine the conformational fluctuations of proteins. In this work, we assess the accuracy of this approach by considering its application to the case of ribonuclease A. We found that the agreement between experimental and calculated chemical shifts improves on average when the chemical shifts are used as replica-averaged restraints with respect to the cases in which X-ray structures or ensembles of structures obtained by standard molecular dynamics simulations are considered.

Protein Dynamics (Cont'd)

Coarse-grained and all-atom modeling of structural states and transitions in hemoglobin

Mustafa Tekpinar and Wenjun Zheng [University at Buffalo]

Proteins: Stru. Fun. & Bioinf., **81**, 240–252, 2013.

Hemoglobin (Hb), an oxygen-binding protein composed of four subunits (α1, α2, β1, and β2), is a well-known example of allosteric proteins that are capable of cooperative ligand binding. Despite decades of studies, the structural basis of its cooperativity remains controversial. In this study, we have integrated coarse-grained (CG) modeling, all-atom simulation, and structural data from X-ray crystallography and wide-angle X-ray scattering (WAXS), aiming to probe dynamic properties of the two structural states of Hb (T and R state) and the transitions between them.

The translocation kinetics of antibiotics through porin OmpC: Insights from structure-based solvation mapping using WaterMap

Que-Tien Tran [Novartis Institutes for BioMedical Research, Inc], Sarah Williams, Ramy Farid, Gül Erdemli and Robert Pearlstein

Proteins: Stru. Fun. & Bioinf., **81**, 291–299, 2013.

Poor permeability of the lipopolysaccharide-based outer membrane of Gram-negative bacteria is compensated by the existence of protein channels (porins) that selectively admit low molecular weight substrates, including many antibiotics. We have previously reported a hypothesis that the costs of transferring protein solvation to and from bulk medium underlie the barriers to protein-ligand association and dissociation, respectively, concomitant with the gain and loss of protein-ligand interactions during those processes. We have now applied this hypothesis to explain the published rates of entry (association) and exit (dissociation) of six antibiotics to/from reconstituted E. coli porin OmpC.

Ligand Binding/Docking

Molecular insight into the inhibition mechanism of cyrtominetin to α-hemolysin by molecular dynamics simulation

Xiaodi Niu, Jiazhang Qiu, Xin Wang, Xiaohan Gao, Jing Dong, Jianfeng Wang, Hongen Li, Yu Zhang, Xiaohan Dai, Chongjian Lu, Xuming Deng [Jilin University]

Europ. Jou. Med. Chem., **60**, 320-328, 2013.

The protein α-hemolysin (α-HL) is a self-assembling exotoxin that binds to the membrane of a susceptible host cell. In this paper, experimental studies show that cyrtominetin (CTM) can inhibit the hemolytic activity of α-HL. To understand how CTM can affect hemolytic activity, molecular dynamics simulations were carried out for α-HL–CTM complex and these results were compared with the crystal structure of monomeric α-HL. With this approach, the analysis revealed that the inhibition of CTM involves CTM directly binding to α-HL.

Studies on the binding modes of Lassa nucleoprotein complexed with m7GpppG and dTTP by molecular dynamic simulations and free energy calculations

Liang Li, Dan Li, Hang Chen & Ju-Guang Han [University of Science and Technology of China]

J. Biomol. Stru. and Dyn., **31**, 299-315, 2013.

Lassa virus can cause dreadful human hemorrhagic disease, for which there is no effective therapy. A recent study points out that the amino (N)-terminal domain of Lassa virus nucleoprotein (NP) plays an important role in viral RNA synthesis and firstly solved the X-ray crystal structures of NP complexed with the capped Deoxythymidine triphosphate (dTTP) analog, but the binding mode of m7GpppG to the N domain of NP, which is required for viral RNA transcription, has not been studied. In this study, molecular dynamics (MD) simulations have been carried out to investigate the characters of dTTP binding to two forms of NP.

Ligand Binding / Docking (Cont'd)

A flexible-protein molecular docking study of the binding of ruthenium complex compounds to PIM1, GSK-3β, and CDK2/Cyclin A protein kinases

Yingting Liu, Neeraj J. Agrawal, Ravi Radhakrishnan [University of Pennsylvania, Philadelphia]

J. Mol.Mod., **19,** 371-382, 2013.

We employ ensemble docking simulations to characterize the interactions of two enantiomeric forms of a Ru-complex compound (1-R and 1-S) with three protein kinases, namely PIM1, GSK-3β, and CDK2/cyclin A. We show that our ensemble docking computational protocol adequately models the structural features of these interactions and discriminates between competing conformational clusters of ligand-bound protein structures. Using the determined X-ray crystal structure of PIM1 complexed to the compound 1-R as a control, we discuss the importance of including the protein flexibility inherent in the ensemble docking protocol, for the accuracy of the structure prediction of the bound state.

Binding to the lipid monolayer induces conformational transition in Aβ monomer

Seongwon Kim, Dmitri K. Klimov [George Mason University]

J. Mol.Mod., **19,** 737-750, 2013.

Using implicit solvent atomistic model and replica exchange molecular dynamics, we study binding of Aβ monomer to zwitterionic dimyristoylphosphatidylcholine (DMPC) lipid monolayer. Our results suggest that Aβ binding to the monolayer is governed primarily by positively charged and aromatic amino acids. Lysine residues tend to interact with surface choline and phosphorous lipid groups, whereas aromatic amino acids penetrate deeper into the monolayer, reaching its hydrophobic core.

Partial activation of α7 nicotinic acetylcholine receptors: insights from molecular dynamics simulations

Caijuan Shi, Rilei Yu, Shengjuan Shao, Yanni Li [Tianjin University]

J. Mol.Mod., **19,** 871-878, 2013.

Nicotinic acetylcholine receptors (nAChRs) are drug targets for neuronal disorders and diseases. Partial agonists for nAChRs are currently being developed as drugs for the treatment of neurological diseases for their relative safety originated from reduced excessive stimulation. In the current study, molecular docking, molecular dynamics simulations and binding energy calculations were performed to theoretically investigate the interactions between the partial agonists, 4-OH-DMXBA and tropisetron with α7-nAChR.

Molecular dynamics and QM/MM-based 3D interaction analyses of cyclin-E inhibitors

Farhan Ahmad Pasha [Institut Français du Pétrole (IFP)], Mohammad Morshed Neaz

J. Mol.Mod., **19,** 879-891, 2013.

Abnormal expression of cyclin-dependent kinase 2 (CDK2)/cyclin-E is detected in colorectal, ovarian, breast and prostate cancers. The study of CDK2 with a bound inhibitor revealed CDK2 as a potential therapeutic target for several proliferative diseases. Several highly selective inhibitors of CDK2 are currently undergoing clinical trials, but possibilities remain for the identification and development of novel and improved inhibitors. A series of 3,5-diaminoindazoles was studied using molecular docking and comparative field analyses. We used post-docking short time molecular dynamics (MD) simulation to account for receptor flexibility.

Ligand Binding / Docking (Cont'd)

The investigations on HIV-1 gp120 bound with BMS-488043 by using docking and molecular dynamics simulations

Liang Li, Hang Chen, Run-Ning Zhao, Ju-Guang Han [University of Science and Technology of China]

J. Mol.Mod., **19,** 905-917, 2013.

BMS-488043, like its predecessor BMS-378806, is a small molecule that can block the interactions between gp120 and CD4, and has shown good clinical efficacy. However, the crystal structure of drug-gp120 complexes or the full-length gp120 free of bound ligand is unpublished until now. Docking combined with molecular dynamics simulation is used to investigate the binding mode between BMS-488043 and gp120. On the basis of the analysis of the simulated results, the plausible binding mode is acquired, such as the changes of binding mode in the trajectory and the calculated binding free energy.

Binding structures of tri-N-acetyl-β-glucosamine in hen egg white lysozyme using molecular dynamics with a polarizable force field

Yang Zhong and Sandeep Patel [University of Delaware]

J. Comp. Chem., **34**, 163–174, 2013.

Lysozyme is a well-studied enzyme that hydrolyzes the β-(1,4)-glycosidic linkage of N-acetyl-β-glucosamine $(NAG)_n$ oligomers. The active site of hen egg-white lysozyme (HEWL) is believed to consist of six subsites, A-F that can accommodate six sugar residues. We present studies exploring the use of polarizable force fields in conjunction with all-atom molecular dynamics (MD) simulations to analyze binding structures of complexes of lysozyme and NAG trisaccharide, $(NAG)_3$.

Structural analysis of the inhibition of APRIL by TACI and BCMA through molecular dynamics simulations

Maite González-Mendióroz, Ana Belén Álvarez-Vázquez, Jaime Rubio-Martinez [University of Barcelona]

J. Mol.Graph. and Mod., **39,** 13-22, 2013.

APRIL (a proliferation-inducing ligand) is a member of the tumour necrosis factor (TNF) superfamily that binds the receptors (TNFRs) TACI and BCMA. Since it was discovered, a great amount of evidence has been reported about the involvement of APRIL in autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS) and multiple sclerosis (MS). The design of compounds mimicking the inhibition of APRIL by its receptors appears to be a promising way to treat autoimmune and cancer diseases. As a first step to achieve these goals and in order to better understand the key interactions involved in these systems, we report a structural analysis of the inhibition of human and murine APRIL by its human receptors TACI and BCMA obtained by MD simulations.

Association of nicotinic acid with a poly(amidoamine) dendrimer studied by molecular dynamics simulations

Julio Caballero [Universidad de Talca], Horacio Poblete, Cristell Navarro, Jans H. Alzate-Morales

J. Mol.Graph. and Mod., **39,** 71-78, 2013.

The interaction of poly(amidoamine)-G3 (PAMAM-G3) dendrimer with nicotinic acid (NA) was investigated by using MD simulations. First, sample free energy profiles of NA crossing PAMAM-G3 at pH 6 and 3 were computed using the adaptive biasing force (ABF) method. We found that PAMAM-G3 provides a more appropriate environment for NA inclusion when internal tertiary amine groups are unprotonated (at pH 6). However, when internal tertiary amine groups are protonated (at pH 3), the PAMAM cavities are less hydrophobic; therefore the drug–dendrimer interactions become similar to drug–solvent interactions.

Ligand Binding / Docking (Cont'd)

Mapping the Functional Binding Sites of Cholesterol in β_2-Adrenergic Receptor by Long-Time Molecular Dynamics Simulations

Xiaohui Cang, Yun Du, Yanyan Mao, Yuanyuan Wang, Huaiyu Yang, and Hualiang Jiang [Chinese Academy of Sciences]

J. Phys. Chem. B., **117**, 1085–1094, 2013**.**

Cholesterol, an abundant membrane component in both lipid rafts and caveolae of cell membrane, plays a crucial role in regulating the function and organization of various G-protein coupled receptors (GPCRs). However, the underlying mechanism for cholesterol-GPCR interaction is still unclear. To this end, we performed a series of microsecond molecular dynamics (MD) simulations on β_2-adrenergic receptor (β_2AR) in the presence and absence of cholesterol molecules in the POPC bilayer.

A!

How maltose influences structural changes to bind to maltose-binding protein: Results from umbrella sampling simulation

Nahren Manuel Mascarenhas and Johannes Kästner [University of Stuttgart]

Proteins: Stru. Fun. & Bioinf., **81**, 185–198, 2013.

A well-studied periplasmic-binding protein involved in the abstraction of maltose is maltose-binding protein (MBP), which undergoes a ligand-induced conformational transition from an open (ligand-free) to a closed (ligand-bound) state. Umbrella sampling simulations have been us to estimate the free energy of binding of maltose to MBP and to trace the potential of mean force of the unbinding event using the center-of-mass distance between the protein and ligand as the reaction coordinate.

Computational protein design suggests that human PCNA-partner interactions are not optimized for affinity

Yearit Fridman, Eyal Gur, Sarel J. Fleishman [Weizmann Institute of Science] and Amir Aharoni

Proteins: Stru. Fun. & Bioinf., **81**, 341–348, 2013.

Increasing the affinity of binding proteins is invaluable for basic and applied biological research. Currently, directed protein evolution experiments are the main approach for generating such proteins through the construction and screening of large mutant libraries. Proliferating cell nuclear antigen (PCNA) is an essential hub protein that interacts with many different partners to tightly regulate DNA replication and repair in all eukaryotes. Here, we used computational design to generate human PCNA mutants with enhanced affinity for several different partners.

Enzyme Catalysis

Calculation of Vibrational Shifts of Nitrile Probes in the Active Site of Ketosteroid Isomerase upon Ligand Binding

Joshua P. Layfield and Sharon Hammes-Schiffer [University of Illinois at Urbana-Champaign]

J. Am. Chem. Soc., **135**, 717–725, 2013.

The vibrational Stark effect provides insight into the roles of hydrogen bonding, electrostatics, and conformational motions in enzyme catalysis. In a recent application of this approach to the enzyme ketosteroid isomerase (KSI), thiocyanate probes were introduced in site-specific positions throughout the active site. This paper implements a quantum mechanical/molecular mechanical (QM/MM) approach for calculating the vibrational shifts of nitrile (CN) probes in proteins. This methodology is shown to reproduce the experimentally measured vibrational shifts upon binding of the intermediate analogue equilinen to KSI for two different nitrile probe positions.

Laboratory Evolution of Enantiocomplementary Candida antarctica Lipase B Mutants with Broad Substrate Scope

Qi Wu, Pankaj Soni, and Manfred T. Reetz [Max-Planck-Institut für Kohlenforschung]

J. Am. Chem. Soc., **135**, 1872–1881, 2013.

Candida antarctica lipase B (CALB) is a robust and easily expressed enzyme used widely in academic and industrial laboratories with many different kinds of applications. In fine chemicals production, examples include acylating kinetic resolution of racemic secondary alcohols and amines as well as desymmetrization of prochiral diols (or the reverse hydrolytic reactions). However, in the case of hydrolytic kinetic resolution of esters or esterifying kinetic resolution of acids in which chirality resides in the carboxylic acid part of the substrate, rate and stereoselectivity are generally poor. In the present study, directed evolution based on iterative saturation mutagenesis was applied to solve the latter problem.

Modeling the structure and proton transfer pathways of the mutant His-107-Tyr of human carbonic anhydrase II

Puspita Halder, Srabani Taraphder [Indian Institute of Technology, Kharagpur]

J. Mol.Mod., **19,** 289-298, 2013.

We present molecular modeling of the structure and possible proton transfer pathways from the surface of the protein to the zinc-bound water molecule in the active site of the mutant His-107–Tyr of human carbonic anhydrase II (HCAII). No high-resolution structure or crystal structure is available till now for this particular mutant due to its lack of stability at physiological temperature. Our analysis utilizes as starting point a series of structures derived from high-resolution crystal structure of the wild type protein. While many of the structures investigated do not reveal a complete path between the zinc bound water and His-64, several others do indicate the presence of a transient connection even when His-64 is present in its outward conformation.

Enzyme Catalysis (Cont'd)

Insight into substituent effects in Cal-B catalyzed transesterification by combining experimental and theoretical approaches

Zhong Ni, Xianfu Lin [Zhejiang University, Hangzhou]

J. Mol.Mod., **19,** 349-358, 2013.

Candida antarctica lipase B (Cal-B) is one of the most recognized biocatalysts because of its high degree of selectivity in a broad range of synthetic applications of industrial importance. Herein, the substituent effects involved in transesterification catalyzed by Cal-B are explored in detail using a combination of experimental analysis and theoretical modeling. The transesterification ability of Cal-B was experimentally determined with 22 vinyl ester analogs and ribavirin as substrates and, on this basis, a series of quantitative structure-activity relationship (QSAR) models are developed using various structural parameters characterizing the variation in substituent groups of the substrate molecules.

Molecular and structural insight into plasmodium falciparum RIO2 kinase

Devendra K. Chouhan, Ashoke Sharon, Chandralata Bal [Birla Institute of Technology, Mesra]

J. Mol.Mod., **19,** 485-496, 2013.

Among approximately 65 kinases of the malarial genome, RIO2 (right open reading frame) kinase belonging to the atypical class of kinase is unique because along with a kinase domain, it has a highly conserved N-terminal winged helix (wHTH) domain. The wHTH domain resembles the wing like domain found in DNA binding proteins and is situated near to the kinase domain. Ligand binding to this domain may reposition the kinase domain leading to inhibition of enzyme function and could be utilized as a novel allosteric site to design inhibitor. In the present study, we have generated a model of RIO2 kinase from Plasmodium falciparum utilizing multiple modeling, simulation approach.

Molecular docking and dynamics simulations of A.niger RNase from Aspergillus niger ATCC26550: for potential prevention of human cancer

Gundampati Ravi Kumar [Banaras Hindu University, Varanasi], Rajasekhar Chikati, Santhi Latha Pandrangi, Manoj Kandapal, Kirti Sonkar, Neeraj Gupta, Chaitanya Mulakayala, Medicherla V. Jagannadham, Chitta Suresh Kumar, Sunita Saxena, Mira Debnath Das

J. Mol.Mod., **19,** 613-621, 2013.

The aim of the present research was to study the anticancer effects of Aspergillus niger (A.niger) RNase. We found that RNase (A.niger RNase) significantly and dose dependently inhibited invasiveness of breast cancer cell line MDA MB 231 by 55 % ($P < 0.01$) at 1 μM concentration. At a concentration of 2 μM, the anti invasive effect of the enzyme increased to 90 % ($P < 0.002$). Keeping the aim to determine molecular level interactions (molecular simulations and protein docking) of human actin with A.niger RNase we extended our work in-vitro to in-silico studies.

Enzyme Catalysis (Cont'd)

Molecular dynamics analysis of a series of 22 potential farnesyltransferase substrates containing a CaaX-motif

Sérgio F. Sousa, João T. S. Coimbra, Diogo Paramos, Rita Pinto, Rodrigo S. Guimarães, Vitor Teixeira, Pedro A. Fernandes, Maria J. Ramos [Universidade do Porto]

J. Mol.Mod., **19,** 673-688, 2013.

Protein farnesyltransferase (FTase) is an important target in many research fields, more markedly so in cancer investigation since several proteins known to be involved in human cancer development are thought to serve as substrates for FTase and to require farnesylation for proper biological activity. Several FTase inhibitors (FTIs) have advanced into clinical testing. Nevertheless, despite the progress in the field several functional and mechanistic doubts on the FTase catalytic activity have persisted. This work provides some crucial information on this important enzyme by describing the application of molecular dynamics simulations using specifically designed molecular mechanical parameters for a variety of 22 CaaX peptides known to work as natural substrates or inhibitors for this enzyme.

Quantum chemistry studies of the catalysis mechanism differences between the two isoforms of glutamic acid decarboxylase

Chunling Wang, Rongxiu Zhu, Hainan Sun, Baiqing Li [Shandong University]

J. Mol.Mod., **19,** 705-714, 2013.

The production of gamma-aminobutyric acid (GABA) is catalyzed by two isoforms of glutamic acid decarboxylase (GAD), using pyridoxal 5′-phosphate (PLP) as the cofactor. Between the two enzymes, GAD67 accounts for normal GABA requirement, while GAD65 stays inactive until emergent demand for GABA. Recent crystal structure findings revealed that the distinct conformation of a common catalytic loop of the enzymes may account for their different functions (Fenalti et al Nat Struct Mol Biol, 14:280-286, 2007). Enlightened by their inferences, we studied the underlying reaction mechanism of the two GAD isoforms using density functional theory (DFT).

Computational study of the effects of protein tyrosine nitrations on the catalytic activity of human thymidylate synthase

Adam Jarmuła [Polish Academy of Sciences], Wojciech Rode

J. Comp. Aided Mol. Des.,**27**, 45-66, 2013.

Tyrosine nitration is a widespread post-translational modification capable of affecting both the function and structure of the host protein molecule. Enzyme thymidylate synthase (TS), a homodimer, is a molecular target for anticancer therapy. Recently purified TS preparations, isolated from mammalian tissues, were found to be nitrated, suggesting this modification to appear endogenously in normal and tumor tissues. In the present paper, combined computational approach, including molecular and essential dynamics and free energy computations, was used to predict the influence on the activity of hTS of nitration of each of the seven tyrosine residues.

Enzyme Catalysis (Cont'd)

Theoretical studies on the common catalytic mechanism of transketolase by using simplified models

Xiang Sheng, Yongjun Liu [Shandong University], Chengbu Liu

J. Mol.Graph. and Mod., **39,** 23-28, 2013.

Transketolase is a convenient model system to study enzymatic thiamin catalysis. By using density functional theory (DFT) method, the transfer mechanism of a 2-carbon fragment between a donor ketose X5P and an acceptor aldose R5P catalyzed by transketolase has been studied on simplified models. The calculation results indicate that the whole reaction cycle contains several proton transfer processes as well as C—C bond formation and cleavage steps. Each C—C bond formation or cleavage step is always accompanied by a proton transfer process, which follows a concerted but asynchronous mechanism.

An in silico approach to evaluate the polyspecificity of methionyl-tRNA synthetases

Saravanan Prabhu Nadarajan, Sam Mathew, Kanagavel Deepankumar, Hyungdon Yun [Yeungnam University]

J. Mol.Graph. and Mod., **39,** 79-86, 2013.

Residue-specific incorporation is a technique used to replace natural amino acids with their close structural analogs, unnatural amino acids (UAAs), during protein synthesis. This is achieved by exploiting the substrate promiscuity of the wild type amino acyl tRNA synthetase (AARS) towards the close structural analogs of their cognate amino acids. In the past few decades, seleno-methionine was incorporated into proteins, using the substrate promiscuity of wild type AARSs, to resolve their crystal structures.

ONIOM (DFT:MM) Study of the Catalytic Mechanism of myo-Inositol Monophosphatase: Essential Role of Water in Enzyme Catalysis in the Two-Metal Mechanism

Xiaoqing Wang and Hajime Hirao [Nanyang Technological University]

J. Phys. Chem. B., **117**, 833–842, 2013**.**

myo-Inositol monophosphatase (IMPase), a putative target of lithium therapy for bipolar disorder, is an enzyme that catalyzes the hydrolysis of myo-inositol-1-phosphate (Ins(1)P) into myo-inositol (MI) and inorganic phosphate. It is known that either two or three Mg^{2+} ions are used as cofactors in IMPase catalysis; however, the detailed catalytic mechanism and the specific number of Mg^{2+} ions required have long remained obscure. To obtain a clearer view of the IMPase reaction, we undertook extensive ONIOM hybrid quantum mechanics and molecular mechanics (QM/MM) calculations, to evaluate the reaction with either three or two Mg^{2+} ions.

Determinants of Regioselectivity and Chemoselectivity in Fosfomycin Resistance Protein FosA from QM/MM Calculations

Rong-Zhen Liao and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Phys. Chem. B., **117**, 1326–1336, 2013**.**

FosA is a manganese-dependent enzyme that utilizes a Mn^{2+} ion to catalyze the inactivation of the fosfomycin antibiotic by glutathione (GSH) addition. We report a theoretical study on the catalytic mechanism and the factors governing the regioselectivity and chemoselectivity of FosA. Density functional theory (DFT) calculations on the uncatalyzed reaction give high barriers and almost no regioselectivity even when adding two water molecules to assist the proton transfer.

A!

Protein-Protein Interactions

Modeling Protein–Protein Recognition in Solution Using the Coarse-Grained Force Field SCORPION

Nathalie Basdevant [Université d'Evry-Val-d'Essonne], Daniel Borgis, and Tap Ha-Duong

J. Chem. Theor. and Comp, **9**, 803–813, 2013.

We present here the SCORPION—Solvated COaRse-grained Protein interactION—force field, a physics-based simplified coarse-grained (CG) force field. It combines our previous CG protein model and a novel particle-based water model which makes it suitable for Molecular Dynamics (MD) simulations of protein association processes. The protein model in SCORPION represents each amino acid with one to three beads, for which electrostatic and van der Waals effective interactions are fitted separately to reproduce those of the all-atom AMBER force field.

Membrane Proteins and Lipid Peptide Interactions

Three-Dimensional Stress Field around a Membrane Protein: Atomistic and Coarse-Grained Simulation Analysis of Gramicidin A

Jejoong Yoo, Qiang Cui [University of Wisconsin]

Biophysical Journal. **104**, 117-127, 2013.

Using both atomistic and coarse-grained (CG) models, we compute the three-dimensional stress field around a gramicidin A (gA) dimer in lipid bilayers that feature different degrees of negative hydrophobic mismatch. The general trends in the computed stress field are similar at the atomistic and CG levels, supporting the use of the CG model for analyzing the mechanical features of protein/lipid/water interfaces.

Membrane-Mediated Protein-Protein Interactions and Connection to Elastic Models: A Coarse-Grained Simulation Analysis of Gramicidin A Association

Jejoong Yoo, Qiang Cui [University of Wisconsin]

Biophysical Journal. **104**, 128-138, 2013.

To further foster the connection between particle based and continuum mechanics models for membrane mediated biological processes, we carried out coarse-grained (CG) simulations of gramicidin A (gA) dimer association and analyzed the results based on the combination of potential of mean force (PMF) and stress field calculations. Similar to previous studies, we observe that the association of gA dimers depends critically on the degree of hydrophobic mismatch, with the estimated binding free energy of >10 kcal/mol in a distearoylphosphatidylcholine bilayer.

Binding of Serotonin to Lipid Membranes

Günther H. Peters [Technical University of Denmark], Chunhua Wang, Nicolaj Cruys-Bagger, Gustavo F. Velardez, Jesper J. Madsen, and Peter Westh

J. Am. Chem. Soc., **135**, 2164–2171, 2013.

A!

Serotonin (5-hydroxytryptamine, 5-HT) is a prevalent neurotransmitter throughout the animal kingdom. It exerts its effect through the specific binding to the serotonin receptor, but recent research has suggested that neural transmission may also be affected by its nonspecific interactions with the lipid matrix of the synaptic membrane. However, membrane–5-HT interactions remain controversial and superficially investigated. Fundamental knowledge of this interaction appears vital in discussions of putative roles of 5-HT, and we have addressed this by thermodynamic measurements and molecular dynamics (MD) simulations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

An Atomistic Model for Assembly of Transmembrane Domain of T cell Receptor Complex

Satyan Sharma and André H. Juffer [University of Oulu]

J. Am. Chem. Soc., **135**, 2188–2197, 2013.

A!

The T cell receptor (TCR) together with accessory cluster of differentiation 3 (CD3) molecules (TCR–CD3 complex) is a key component in the primary function of T cells. The nature of association of the transmembrane domains is of central importance to the assembly of the complex and is largely unknown. Using multiscale molecular modeling and simulations, we have investigated the structure and assembly of the TCRα–CD3ε–CD3δ transmembrane domains both in membrane and in micelle environments.

Reconciling the Roles of Kinetic and Thermodynamic Factors in Membrane–Protein Insertion

James C. Gumbart, Ivan Teo, Benoît Roux, and Klaus Schulten [University of Illinois at Urbana−Champaign]

J. Am. Chem. Soc., **135**, 2291–2297, 2013.

A!

For the vast majority of membrane proteins, insertion into a membrane is not direct, but rather is catalyzed by a protein-conducting channel, the translocon. This channel provides a lateral exit into the bilayer while simultaneously offering a pathway into the aqueous lumen. The determinants of a nascent protein's choice between these two pathways are not comprehensively understood, although both energetic and kinetic factors have been observed. To elucidate the specific roles of some of these factors, we have carried out extensive all-atom molecular dynamics simulations of different nascent transmembrane segments embedded in a ribosome-bound bacterial translocon, SecY.

Cardiolipin Models for Molecular Simulations of Bacterial and Mitochondrial Membranes

Thomas Lemmin, Christophe Bovigny, Diane Lançon, and Matteo Dal Peraro [Ecole Polytechnique Fédérale de Lausanne (EPFL)]

J. Chem. Theor. and Comp, **9**, 670–678, 2013.

Present in bacterial and mitochondrial membranes, cardiolipins have a unique dimeric structure, which carries up to two charges (i.e., one per phosphate group) and, under physiological conditions, can be unprotonated or singly protonated. Exhaustive models and characterization of cardiolipins are to date scarce; therefore we propose an ab initio parametrization of cardiolipin species for molecular simulation consistent with commonly used force fields. Molecular dynamics simulations using these models indicate a protonation dependent lipid packing.

Hybrid Approach for Highly Coarse-Grained Lipid Bilayer Models

Anand Srivastava and Gregory A. Voth [University of Chicago]

J. Chem. Theor. and Comp, **9**, 750–765, 2013.

We present a systematic methodology to develop highly coarse-grained (CG) lipid models for large scale biomembrane simulations, in which we derive CG interactions using a powerful combination of the multiscale coarse-graining (MS-CG) method, and an analytical form of the CG potential to model interactions at short-range. The resulting hybrid coarse-graining (HCG) methodology is used to develop a three-site solvent-free model for 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and a 1:1 mixture of 1,2-dioleoyl-sn-glycero-3-phospho-l-serine (DOPS) and DOPC.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

A consistent description of HYdrogen bond and DEhydration energies in protein–ligand complexes: methods behind the HYDE scoring function

Nadine Schneider, Gudrun Lange, Sally Hindle, Robert Klein, Matthias Rarey[University of Hamburg]

J. Comp. Aided Mol. Des.,**27**, 15-29, 2013.

The estimation of free energy of binding is a key problem in structure-based design. We developed the scoring function HYDE based on a consistent description of HYdrogen bond and DEhydration energies in protein–ligand complexes. HYDE is applicable to all types of protein targets since it is not calibrated on experimental binding affinity data or protein–ligand complexes. The comprehensible atom-based score of HYDE is visualized by applying a very intuitive coloring scheme, thereby facilitating the analysis of protein–ligand complexes in the lead optimization process. In this paper, we have revised several aspects of the former version of HYDE which was described in detail previously.

Binding Competition to the POPG Lipid Bilayer of Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+} in Different Ion Mixtures and Biological Implication

Yanyan Mao, Yun Du, Xiaohui Cang, Jinan Wang, Zhuxi Chen, Huaiyu Yang, and Hualiang Jiang [Chinese Academy of Sciences]

J. Phys. Chem. B., **117**, 850–858, 2013**.**

A!

Ion mixtures are prevalent in both cytosol and the exterior of a plasma membrane with variable compositions and concentrations. Although abundant MD simulations have been performed to study the effects of single ion species on the structures of lipid bilayers, our understanding of the influence of the ion mixture on membranes is still limited; for example, the competition mechanism of different ions in binding with lipids is not clearly addressed yet. Here, microsecond MD simulations were carried out to study the effects of the mixtures of Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+} ions on a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol (POPG) bilayer.

Dendritic Amphiphiles Strongly Affect the Biophysical Properties of DPPC Bilayer Membranes

Riya J. Muckom, Francesca Stanzione, Richard D. Gandour, and Amadeu K. Sum [Colorado School of Mines]

J. Phys. Chem. B., **117**, 1810–1818, 2013**.**

Molecular dynamics (MD) simulations were used to gain insight on the molecular interactions in a model biological membrane comprised of a bilayer with DPPC (dipalmitoylphosphotidylcholine) and antimicrobial dendritic amphiphile molecules [$RCONHC(CH_2CH_2COOH)_3$, where R is the saturated hydrocarbon tail (R = n-C_nH_{2n+1}), to be abbreviated as 3CAmn]. This study analyzes different biophysical properties of the equilibrated mixed bilayers, at 300 and 325 K, to determine how the presence of the 3CAmn, in varying concentrations and tail lengths, affects the lipid bilayer.

Protein Folding

Backtracking due to Residual Structure in the Unfolded State Changes the Folding of the Third Fibronectin Type III Domain from Tenascin-C

Swarnendu Tripathi, George I. Makhatadze, and Angel E. Garcia [Rensselaer Polytechnic Institute]

J. Phys. Chem. B., **117**, 800–810, 2013**.**

Residual structure in the unfolded state of a protein may play a crucial role in folding and stability. In the present study, using an all (heavy)-atom structure based model and replica exchange molecular dynamics simulations, we explored the folding landscape of the third fibronectin type III domain from tenascin-C (TNfn3). Specifically, both the wild type (WT) and a variant with two additional amino acids, Gly-Leu (GL), at the C-terminus (WT_{+GL}) were studied. We found that, although both domains of TNfn3 are topologically frustrated, the early formation of the native contacts from the C-terminal end of WT_{+GL} causes more "backtracking" than in the WT.

Protein-Nucleic acid Interactions

Force Biased Molecular Dynamics Simulation Study of Effect of Dendrimer Generation on Interaction with DNA

Bidisha Nandy, Prabal K. Maiti, and Alex Bunker [Indian Institute of Science, Bangalore]

J. Chem. Theor. and Comp, **9**, 722–729, 2013.

We have studied the effect of dendrimer generation on the interaction between dsDNA and the PAMAM dendrimer using force biased simulation of dsDNA with three generations of dendrimer: G3, G4, and G5. Our results for the potential of mean force (PMF) and the dendrimer asphericity along the binding pathway, combined with visualization of the simulations, demonstrate that dendrimer generation has a pronounced impact on the interaction. The PMF increases linearly with increasing generation of the dendrimer.

A nonredundant structure dataset for benchmarking protein-RNA computational docking

Sheng-You Huang and Xiaoqin Zou [University of Missouri]

J. Comp. Chem., **34**, 311–318, 2013.

Protein–RNA interactions play an important role in many biological processes. The ability to predict the molecular structures of protein–RNA complexes from docking would be valuable for understanding the underlying chemical mechanisms. We have developed a novel nonredundant benchmark dataset for protein–RNA docking and scoring. The diverse dataset of 72 targets consists of 52 unbound–unbound test complexes, and 20 unbound–bound test complexes.

Modeling the zing finger protein SmZF1 from Schistosoma mansoni: Insights into DNA binding and gene regulation

Mainá Bitar, Marcela Gonçalves Drummond, Mauricio Garcia Souza Costa, Francisco Pereira Lobo, Carlos Eduardo Calzavara-Silva, Paulo Mascarello Bisch, Carlos Renato Machado, Andréa Mara Macedo, Raymond J. Pierce, Glória Regina Franco [Universidade Federal de Minas Gerais]

J. Mol.Graph. and Mod., **39,** 29-38, 2013.

Zinc finger proteins are widely found in eukaryotes, representing an important class of DNA-binding proteins frequently involved in transcriptional regulation. Zinc finger motifs are composed by two antiparallel β-strands and one α-helix, stabilized by a zinc ion coordinated by conserved histidine and cysteine residues. In Schistosoma mansoni, these regulatory proteins are known to modulate morphological and physiological changes, having crucial roles in parasite development. We defined a consensus DNA binding sequence using three distinct algorithms and further carried out docking calculations, which revealed the interaction of fingers 2–4 with the predicted DNA.

Nucleic Acids

Free Energy Cost of Stretching mRNA Hairpin Loops Inhibits Small RNA Binding

Yuzhong Meng, Daniel P. Aalberts [Williams College, Williamstown]

Biophysical Journal. **104**, 482-487, 2013.

Small RNA-mRNA binding is an essential step in RNA interference, an important cellular regulatory process. Calculations of binding free energy have been used in binding site prediction, but the cost of stretching the mRNA loop when the small RNA-mRNA duplex forms requires further exploration. Here, using both polymer physics theory and simulations, we estimate the free energy of a stretched mRNA loop.

Quantum-Mechanical Analysis of the Energetic Contributions to π Stacking in Nucleic Acids versus Rise, Twist, and Slide

Trent M. Parker, Edward G. Hohenstein, Robert M. Parrish, Nicholas V. Hud, and C. David Sherrill [Georgia Institute of Technology]

J. Am. Chem. Soc., **135**, 1306–1316, 2013.

Symmetry-adapted perturbation theory (SAPT) is applied to pairs of hydrogen-bonded nucleobases to obtain the energetic components of base stacking (electrostatic, exchange-repulsion, induction/polarization, and London dispersion interactions) and how they vary as a function of the helical parameters Rise, Twist, and Slide. Computed average values of Rise and Twist agree well with experimental data for B-form DNA from the Nucleic Acids Database, even though the model computations omitted the backbone atoms (suggesting that the backbone in B-form DNA is compatible with having the bases adopt their ideal stacking geometries).

Identification and Characterization of New DNA G-Quadruplex Binders Selected by a Combination of Ligand and Structure-Based Virtual Screening Approaches

Stefano Alcaro, Caterina Musetti, Simona Distinto, Margherita Casatti, Giuseppe Zagotto, Anna Artese, Lucia Parrotta, Federica Moraca, Giosuè Costa, Francesco Ortuso, Elias Maccioni, and Claudia Sissi [University of Padova]

J.Med.Chem., **56**, 843–855, 2013.

A!

Nowadays, it has been demonstrated that DNA G-quadruplex arrangements are involved in cellular aging and cancer, thus boosting the discovery of selective binders for these DNA secondary structures. By taking advantage of available structural and biological information on these structures, we performed a high throughput in silico screening of commercially available molecules databases by merging ligand- and structure-based approaches by means of docking experiments. Compounds selected by the virtual screening procedure were then tested for their ability to interact with the human telomeric G-quadruplex folding by circular dichroism, fluorescence spectroscopy, and photodynamic techniques.

DFT investigations of phosphotriesters hydrolysis in aqueous solution: a model for DNA single strand scission induced by N-nitrosoureas

Tingting Liu, Lijiao Zhao [Beijing University of Technology], Rugang Zhong

J. Mol.Mod., **19,** 647-659, 2013.

DNA phosphotriester adducts are common alkylation products of DNA phosphodiester moiety induced by N-nitrosoureas. The 2-hydroxyethyl phosphotriester was reported to hydrolyze more rapidly than other alkyl phosphotriesters both in neutral and in alkaline conditions, which can cause DNA single strand scission. In this work, DFT calculations have been employed to map out the four lowest activation free-energy profiles for neutral and alkaline hydrolysis of triethyl phosphate (TEP) and diethyl 2-hydroxyethyl phosphate (DEHEP).

Nucleic Acids (Cont'd)

A three-layer ONIOM model for the outside binding of cationic porphyrins and nucleotide pair DNA

Gloria I. Cárdenas-Jirón [University of Santiago de Chile], Luis Cortez-Santibañez

J. Mol.Mod., **19,** 811-824, 2013.

In this work we investigated the outside binding mode between a cationic porphyrin and a nucleotide pair of DNA, adenine-thymine and guanine-cytosine, in a supramolecular assembly. We used two structural models (semi-extended, extended) that differ in the size of porphyrin, two kinds of theoretical methods: a three layer ONIOM (B3LYP/6-31G(d)/PM3/UFF), and DFT B3LYP/6-31G(d,p), and three cationic porphyrins. ONIOM method was first tested on the semi-extended model that was calculated in four environments: gas phase, solution phase using an explicit solvent model (H_2O), in the presence of a sodium cation (Na^+) and in both (H_2O + Na^+).

Theoretical Simulations on Interactions of Mono- and Dinuclear Metallonucleases with DNA

Chunmei Liu, Yanyan Zhu, Peipei Chen, and Mingsheng Tang [Zhengzhou University]

J. Phys. Chem. B., **117**, 1197–1209, 2013**.**

In the present study, molecular dynamic simulations have been performed to investigate the DNA binding affinities and cleavage activities of a new class of mononuclear copper (p-Cu(BPA) and m-Cu(BPA)) and dinuclear copper–platinum (p-Cu(BPA)-Pt and m-Cu(BPA)-Pt) metallonucleases. The simulated results reveal that the two mononuclear nucleases are noncovalent minor groove DNA binders and the two dinuclear ones tend to be bound to DNA in the major groove by a covalent bond between the platinum center and N7 of the guanine base, which is in agreement with the experimental results.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Combining QSAR classification models for predictive modeling of human monoamine oxidase inhibitors

Aliuska Morales Helguera, Alfonso Pérez-Garrido, Alexandra Gaspar, Joana Reis, Fernando Cagide, Dolores Vina, M.Natália D.S. Cordeiro, Fernanda Borges [Universidade do Porto]

Europ. Jou. Med. Chem., **59**, 75-90, 2013.

Due to their role in the metabolism of monoamine neurotransmitters, MAO-A and MAO-B present a significant pharmacological interest. For instance the inhibitors of human MAO-B are considered useful tools for the treatment of Parkinson Disease. Therefore, the rational design and synthesis of new MAOs inhibitors is considered of great importance for the development of new and more effective treatments of Parkinson Disease. In this work, Quantitative Structure Activity Relationships (QSAR) has been developed to predict the human MAO inhibitory activity and selectivity.

Quantitative Structure-Activity Relations (Cont'd)

Introducing new dimensions in MIA-QSAR: A case for chemokine receptor inhibitors

Cleiton A. Nunes, Matheus P. Freitas [Federal University of Lavras]

Europ. Jou. Med. Chem., **60**, 297-300, 2013.

Multivariate image analysis applied to quantitative structure–activity relationships (MIA-QSAR) is a very simple correlative method that uses pixels (binaries) of chemical structures built from 2D viewer programs as descriptors; structural changes correspond to different pixel coordinates, which explain the variance in the bioactivities block. The MIA-QSAR method has shown to be predictive and capable of encoding some chemical information, but introduction of more descriptive information, such as atom size and colors to differentiate atom types, would improve predictability and interpretability.

Dependence of QSAR Models on the Selection of Trial Descriptor Sets: A Demonstration Using Nanotoxicity Endpoints of Decorated Nanotubes

Chi-Yu Shao, Sing-Zuo Chen, Bo-Han Su, Yufeng J. Tseng [National Taiwan University], Emilio Xavier Esposito, and Anton J. Hopfinger

J.Chem. Infor. and Mod. **53**, 142–158, 2013.

Little attention has been given to the selection of trial descriptor sets when designing a QSAR analysis even though a great number of descriptor classes, and often a greater number of descriptors within a given class, are now available. This paper reports an effort to explore interrelationships between QSAR models and descriptor sets. Zhou and co-workers (Zhou et al., Nano Lett.**2008**, 8 (3), 859–865) designed, synthesized, and tested a combinatorial library of 80 surface modified, that is decorated, multi-walled carbon nanotubes for their composite nanotoxicity using six endpoints all based on a common 0 to 100 activity scale.

Biomacromolecular quantitative structure–activity relationship (BioQSAR): a proof-of-concept study on the modeling, prediction and interpretation of protein–protein binding affinity

Peng Zhou [University of Electronic Science and Technology of China (UESTC)], Congcong Wang, Feifei Tian, Yanrong Ren, Chao Yang, Jian Huang

J. Comp. Aided Mol. Des.,**27**, 67-78, 2013.

Quantitative structure–activity relationship (QSAR), a regression modeling methodology that establishes statistical correlation between structure feature and apparent behavior for a series of congeneric molecules quantitatively, has been widely used to evaluate the activity, toxicity and property of various small-molecule compounds such as drugs, toxicants and surfactants. However, it is surprising to see that such useful technique has only very limited applications to biomacromolecules, albeit the solved 3D atom-resolution structures of proteins, nucleic acids and their complexes have accumulated rapidly in past decades. Here, we present a proof-of-concept paradigm for the modeling, prediction and interpretation of the binding affinity of 144 sequence-nonredundant, structure-available and affinity-known protein complexes (Kastritis et al. Protein Sci 20:482–491, 2011) using a biomacromolecular QSAR (BioQSAR) scheme.

Potentials and Parameters

Optimization of parameters for semiempirical methods VI: more modifications to the NDDO approximations and re-optimization of parameters

James J. P. Stewart [Stewart Computational Chemistry]

J. Mol.Mod., **19,** 1-32, 2013.

Modern semiempirical methods are of sufficient accuracy when used in the modeling of molecules of the same type as used as reference data in the parameterization. Outside that subset, however, there is an abundance of evidence that these methods are of very limited utility. In an attempt to expand the range of applicability, a new method called PM7 has been developed. PM7 was parameterized using experimental and high-level ab initio reference data, augmented by a new type of reference data intended to better define the structure of parameter space.

Coarse-Grained Potentials for Local Interactions in Unfolded Proteins

Ali Ghavami, Erik van der Giessen, and Patrick R. Onck [University of Groningen]

J. Chem. Theor. and Comp, **9**, 432–440, 2013.

Recent studies have revealed the key role of natively unfolded proteins in many important biological processes. In order to study the conformational changes of these proteins, a one-bead-per-amino-acid coarse grained (CG) model is developed, and a method is proposed to extract the potential functions for the local interactions between CG beads. Experimentally obtained Ramachandran data for the coil regions of proteins are converted into distributions of pseudo-bond and pseudo-dihedral angles between neighboring alpha-carbons in the polypeptide chain.

Improved Parameters for the Martini Coarse-Grained Protein Force Field

Djurre H. de Jong, Gurpreet Singh, W. F. Drew Bennett, Clement Arnarez, Tsjerk A. Wassenaar, Lars V. Schäfer, Xavier Periole, D. Peter Tieleman, and Siewert J. Marrink [University of Groningen]

J. Chem. Theor. and Comp, **9**, 687–697, 2013.

The Martini coarse-grained force field has been successfully used for simulating a wide range of (bio)molecular systems. Recent progress in our ability to test the model against fully atomistic force fields, however, has revealed some shortcomings. Most notable, phenylalanine and proline were too hydrophobic, and dimers formed by polar residues in apolar solvents did not bind strongly enough. Here, we reparametrize these residues either through reassignment of particle types or by introducing embedded charges.

Molecular Dynamics

Principal component and clustering analysis on molecular dynamics data of the ribosomal L11·23S subdomain

Antje Wolf, Karl N. Kirschner [Fraunhofer-Institute for Algorithms and Scientific Computing (SCAI)]

J. Mol.Mod., **19,** 539-549, 2013.

With improvements in computer speed and algorithm efficiency, MD simulations are sampling larger amounts of molecular and biomolecular conformations. Being able to qualitatively and quantitatively sift these conformations into meaningful groups is a difficult and important task, especially when considering the structure-activity paradigm. Here we present a study that combines two popular techniques, principal component (PC) analysis and clustering, for revealing major conformational changes that occur in molecular dynamics (MD) simulations.

Molecular Dynamics (Cont'd)

Coarse-grained simulations for organic molecular liquids based on Gay-Berne and electric multipole potentials

Peijun Xu, Hujun Shen, Lu Yang, Yang Ding, Beibei Li, Ying Shao, Yingchen Mao, Guohui Li [Chinese Academy of Sciences, Dalian]

J. Mol.Mod., **19,** 551-558, 2013.

Coarse-grained studies of CH_3SH, CH_3CHO and $CHCl_3$ liquids, based on anisotropic Gay-Berne (GB) and electric multipole potentials (EMP), demonstrate that the coarse-grained model is able to qualitatively reproduce the results obtained from the atomistic model (AMOEBA polarizable force field) and allows for significant saving in computation time. It should be pointed out that the accuracy of the coarse-grained model is very sensitive to how well the anisotropic GB particle is defined and how satisfactorily the EMP sites are chosen.

How to Improve Docking Accuracy of AutoDock4.2: A Case Study Using Different Electrostatic Potentials

Xuben Hou, Jintong Du, Jian Zhang, Lupei Du, Hao Fang, and Minyong Li [Shandong University]

J.Chem. Infor. and Mod. **53**, 188–200, 2013.

Molecular docking, which is the indispensable emphasis in predicting binding conformations and energies of ligands to receptors, constructs the high-throughput virtual screening available. So far, increasingly numerous molecular docking programs have been released, and among them, AutoDock 4.2 is a widely used docking program with exceptional accuracy. In this paper, nine different charge-assigning methods, including AM1-BCC, Del-Re, formal, Gasteiger–Hückel, Gasteiger–Marsili, Hückel, Merck molecular force field (MMFF), and Pullman, as well as the ab initio Hartree–Fock charge, were sufficiently explored for their molecular docking performance by using AutoDock4.2.

Solution structures of polcalcin Phl p 7 in three ligation states: Apo-, hemi-Mg^{2+}-bound, and fully Ca^{2+}-bound

Michael T. Henzl [University of Missouri], Arthur G. Sirianni, Wei G. Wycoff, Anmin Tan and John J. Tanner

Proteins: Stru. Fun. & Bioinf., **81**, 300–315, 2013.

Polcalcins are small EF-hand proteins believed to assist in regulating pollen-tube growth. Phl p 7, from timothy grass (Phleum pratense), crystallizes as a domain-swapped dimer at low pH. This study describes the solution structures of the recombinant protein in buffered saline at pH 6.0, containing either 5.0 mM EDTA, 5.0 mM Mg^{2+}, or 100 μM Ca^{2+}. Phl p 7 is monomeric in all three ligation states. In the apo-form, both EF-hand motifs reside in the closed conformation, with roughly antiparallel N- and C-terminal helical segments.

Free Energy Perturbation

w-REXAMD: A Hamiltonian Replica Exchange Approach to Improve Free Energy Calculations for Systems with Kinetically Trapped Conformations

Mehrnoosh Arrar [University of California San Diego], Cesar Augusto F. de Oliveira, Mikolai Fajer, William Sinko, and J. Andrew McCammon

J. Chem. Theor. and Comp, **9**, 18–23, 2013.

Free energy governs the equilibrium extent of many biological processes. High barriers separating free energy minima often limit the sampling in molecular dynamics (MD) simulations, leading to inaccurate free energies. Here, we demonstrate enhanced sampling and improved free energy calculations, relative to conventional MD, using windowed accelerated MD within a Hamiltonian replica exchange framework (w-REXAMD). We show that for a case in which multiple conformations are separated by large free energy barriers, w-REXAMD is a useful enhanced sampling technique, without any necessary reweighting.

Free Energy Perturbation (Cont'd)

A New Maximum Likelihood Approach for Free Energy Profile Construction from Molecular Simulations

Tai-Sung Lee, Brian K. Radak, Anna Pabis, and Darrin M. York [Rutgers University]

J. Chem. Theor. and Comp, **9**, 153–164, 2013.

A!

A novel variational method for construction of free energy profiles from molecular simulation data is presented. The variational free energy profile (VFEP) method uses the maximum likelihood principle applied to the global free energy profile based on the entire set of simulation data (e.g., from multiple biased simulations) that spans the free energy surface. The new method addresses common obstacles in two major problems usually observed in traditional methods for estimating free energy surfaces: the need for overlap in the reweighting procedure and the problem of data representation.

Ions and RNAs: Free Energies of Counterion-Mediated RNA Fold Stabilities

C. H. Mak [University of Southern California] and Paul S. Henke

J. Chem. Theor. and Comp, **9**, 621–639, 2013.

We present an implicit ion model for the calculation of the electrostatic free energies of RNA conformations in the presence of divalent counterions such as Mg^{2+}. The model was applied to the native and several non-native structures of the hammerhead ribozyme and the group I intron in Tetrahymena to study the stability of candidate unfolding intermediates. Based on a rigorous statistical mechanical treatment of the counterions that are closely associated with the RNA while handling the rest of the ions in the solution via a mean field theory in the Grand Canonical ensemble, the implicit ion model accurately reproduces the ordering of their free energies.

Standard Binding Free Energies from Computer Simulations: What Is the Best Strategy?

James C. Gumbart, Benoît Roux [Argonne National Laboratory], and Christophe Chipot

J. Chem. Theor. and Comp, **9**, 794–802, 2013.

A!

Accurate prediction of standard binding free energies describing protein–ligand association remains a daunting computational endeavor. Here, two distinct avenues to determine the standard binding free energy are compared in the case of a short, proline-rich peptide associating to the Src homology domain 3 of tyrosine kinase Abl. These avenues, one relying upon alchemical transformations and the other on potentials of mean force (PMFs), invoke a series of geometrical restraints acting on collective variables designed to alleviate sampling limitations inherent to classical molecular dynamics simulations.

Comparison of two simulation methods to compute solvation free energies and partition coefficients

Li Yang, Alauddin Ahmed and Stanley I. Sandler [University of Delaware]

J. Comp. Chem., **34**, 284–293, 2013.

The thermodynamic integration (TI) and expanded ensemble (EE) methods are used here to calculate the hydration free energy in water, the solvation free energy in 1-octanol, and the octanol-water partition coefficient for a six compounds of varying functionality using the optimized potentials for liquid simulations (OPLS) all-atom (AA) force field parameters and atomic charges. Both methods use the molecular dynamics algorithm as a primary component of the simulation protocol, and both have found wide applications in fields such as the calculation of activity coefficients, phase behavior, and partition coefficients.

QM and QM/MM

An Ionic Liquid Dependent Mechanism for Base Catalyzed β-Elimination Reactions from QM/MM Simulations

Caley Allen, Somisetti V. Sambasivarao, and Orlando Acevedo [Auburn University, Auburn]

J. Am. Chem. Soc., **135**, 1065–1072, 2013.

Ionic liquids have been proposed to induce a mechanistic change in the reaction pathway for the fundamentally important base-induced β-elimination class compared to conventional solvents. The role of the reaction medium in the elimination of 1,1,1-tribromo-2,2-bis(3,4-dimethoxyphenyl)ethane via two bases, piperidine and pyrrolidine, has been computationally investigated using methanol and the ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate and hexafluorophosphate [BMIM][BF_4] and [BMIM][PF_6], respectively.

Sequence selectivity of azinomycin B in DNA alkylation and cross-linking: a QM/MM study

Dhurairajan Senthilnathan, Anbarasan Kalaiselvan, Ponnambalam Venuvanalingam [Bharathidasan University]

J. Mol.Mod., **19,** 383-390, 2013.

Azinomycin B—a well-known antitumor drug—forms cross-links with DNA through alkylation of purine bases and blocks tumor cell growth. This reaction has been modeled using the ONIOM (B3LYP/6-31 + g(d):UFF) method to understand the mechanism and sequence selectivity. ONIOM results have been checked for reliability by comparing them with full quantum mechanics calculations for selected paths. Calculations reveal that, among the purine bases, guanine is more reactive and is alkylated by aziridine ring through the C10 position, followed by alkylation of the epoxide ring through the C21 position of Azinomycin B.

Low-energy conformers of pamidronate and their intramolecular hydrogen bonds: a DFT and QTAIM study

Masoud Arabieh, Mohammad Hossein Karimi-Jafari [Shahid Beheshti University], Mohammad Ghannadi-Maragheh

J. Mol.Mod., **19,** 427-438, 2013.

Extensive DFT and ab initio calculations were performed to characterize the conformational space of pamidronate, a typical pharmaceutical for bone diseases. Mono-, di- and tri-protic states of molecule, relevant for physiological pH range, were investigated for both canonical and zwitterionic tautomers. Semiempirical PM6 method were used for prescreening of the single bond rotamers followed by geometry optimizations at the B3LYP/6-31++G(d,p) and B3LYP/6-311++G(d,p) levels. For numerous identified low energy conformers the final electronic energies were determined at the MP2/6-311++G(2df,2p) level and corrected for thermal effects at B3LYP level.

Prodrugs of fumarate esters for the treatment of psoriasis and multiple sclerosis—a computational approach

Rafik Karaman [Al-Quds University], Ghadeer Dokmak, Maryam Bader, Hussein Hallak, Mustafa Khamis, Laura Scrano, Sabino Aurelio Bufo

J. Mol.Mod., **19,** 439-452, 2013.

Density functional theory (DFT) calculations at B3LYP/6-31 G (d,p) and B3LYP/6-311 + G(d,p) levels for the substituted pyridine-catalyzed isomerization of monomethyl maleate revealed that isomerization proceeds via four steps, with the rate-limiting step being proton transfer from the substituted pyridinium ion to the C=C double bond in INT1. In addition, it was found that the isomerization rate (maleate to fumarate) is solvent dependent. Polar solvents, such as water, tend to accelerate the isomerization rate, whereas apolar solvents, such as chloroform, act to slow down the reaction.

QM and QM/MM (Cont'd)

Hydrogen bonds in galactopyranoside and glucopyranoside: a density functional theory study

Zahrabatoul Mosapour Kotena [University of Malaya], Reza Behjatmanesh-Ardakani, Rauzah Hashim, Vijayan Manickam Achari

J. Mol.Mod., **19,** 589-599, 2013.

Density functional theory calculations on two glycosides, namely, n-octyl-β-D-glucopyranoside (C_8O-β-Glc) and n-octyl-β-D-galactopyranoside (C_8O-β-Gal) were performed for geometry optimization at the B3LYP/6-31G level. Both molecules are stereoisomers (epimers) differing only in the orientation of the hydroxyl group at the C4 position. Thus it is interesting to investigate electronically the effect of the direction (axial/equatorial) of the hydroxyl group at the C4 position. The structure parameters of X-H···Y intramolecular hydrogen bonds were analyzed, while the nature of these bonds and the intramolecular interactions were considered using the atoms in molecules (AIM) approach.

QM study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent

Ramin Miri, Nima Razzaghi-asl, Mohammad K. Mohammadi [Islamic Azad University]

J. Mol.Mod., **19,** 727-735, 2013.

Isatin is an important compound from the biological aspect of view. It is an endogenous substance and moreover; various pharmacological activities have been reported for isatin and its derivatives. In-vitro cytotoxic effects of the prepared isatin Schiff bases toward HeLa, LS180 and Raji human cancer cell lines has been reported in our previous work. 3-(2-(4-nitrophenyl)hydrazono) indolin-2-one was found to be the most potent one among the studied compounds (IC_{30} = 12.2 and 21.8 μM in HeLa and LS-180 cell lines, respectively).

Is it possible for Fe^{2+} to approach protoporphyrin IX from the side of Tyr-13 in Bacillus subtilis ferrochelatase? An answer from QM/MM study

Yaxue Wang, Yong Shen [Sun Yat-sen University]

J. Mol.Mod., **19,** 963-971, 2013.

We previously reported the insertion process of the ferrous ion into the protoporphyrin IX from the side of the residue His-183 (J. Inorg. Biochem. 103 (2009) 1680–1686). Sellers et al. suggested that the ferrous ion probably approaches the protoporphyrin IX via the opposite side in the human enzyme. In this paper, we simulated the insertion process of Fe^{2+} into the protoporphyrin IX from the side of the residue Tyr-13 at the opposite site of His-183 by QM/MM method on Bacillus subtilis ferrochelatase.

Liquid Methanol from DFT and DFT/MM Molecular Dynamics Simulations

Nicolas Sieffert [Université Joseph Fourier Grenoble I], Michael Bühl, Marie-Pierre Gaigeot, and Carole A. Morrison

J. Chem. Theor. and Comp, **9**, 106–118, 2013.

We present a comparative study of computational protocols for the description of liquid methanol from ab initio molecular dynamics simulations, in view of further applications directed at the modeling of chemical reactivity of organic and organometallic molecules in (explicit) methanol solution. We tested density functional theory molecular dynamics (DFT-MD) in its Car–Parrinello Molecular Dynamics (CPMD) and Quickstep/Born–Oppenheimer MD (CP2K) implementations, employing six popular density functionals with and without corrections for dispersion interactions (namely BLYP, BLYP-D2, BLYP-D3, BP86, BP86-D2, and B97-D2).

QM and QM/MM (Cont'd)

Accurate and Efficient Treatment of Continuous Solute Charge Density in the Mean-Field QM/MM Free Energy Calculation

Hiroshi Nakano and Takeshi Yamamoto [Kyoto University]

J. Chem. Theor. and Comp, **9**, 188–203, 2013.

QM/MM free energy calculation is computationally demanding because of the need for an excessive number of electronic structure calculations. A practical approach for reducing the computational cost is that based on mean field approximation, which calculates the QM wave function in the presence of a partially or totally averaged potential of the MM environment. For obtaining the latter potential, it is common to first represent the QM molecule in terms of point charges and then perform statistical sampling of MM molecules. In this paper, we thus consider a more accurate and robust implementation of mean-field QM/MM method based on continuous QM charge density.

Accurate Reaction Energies in Proteins Obtained by Combining QM/MM and Large QM Calculations

LiHong Hu, Pär Söderhjelm, and Ulf Ryde [Lund University]

J. Chem. Theor. and Comp, **9**, 640–649, 2013.

We here suggest and test a new method to obtain stable energies in proteins for charge-neutral reactions by running large quantum mechanical (QM) calculations on structures obtained by combined QM and molecular mechanics (QM/MM) geometry optimization on several snapshots from molecular dynamics simulations. As a test case, we use a proton transfer between a metal-bound cysteine residue and a second-sphere histidine residue in the active site of [Ni,Fe] hydrogenase, which has been shown to be very sensitive to the surroundings.

Fluorescence of Tryptophan in Designed Hairpin and Trp-Cage Miniproteins: Measurements of Fluorescence Yields and Calculations by Quantum Mechanical Molecular Dynamics Simulations

Andrew W. McMillan, Brandon L. Kier, Irene Shu, Aimee Byrne, Niels H. Andersen, and William W. Parson [University of Washington, Seattle]

J. Phys. Chem. B., **117**, 1790–1809, 2013**.**

The quantum yield of tryptophan (Trp) fluorescence was measured in 30 designed miniproteins (17 β-hairpins and 13 Trp-cage peptides), each containing a single Trp residue. Measurements were made in D_2O and H_2O to distinguish between fluorescence quenching mechanisms involving electron and proton transfer in the hairpin peptides, and at two temperatures to check for effects of partial unfolding of the Trp-cage peptides. The extent of folding of all the peptides also was measured by NMR. The fluorescence yields ranged from 0.01 in some of the Trp-cage peptides to 0.27 in some hairpins.

Comparative or Homology Modeling

Assignment of Pterin Deaminase Activity to an Enzyme of Unknown Function Guided by Homology Modeling and Docking

Hao Fan, Daniel S. Hitchcock, Ronald D. Seidel, II, Brandan Hillerich, Henry Lin, Steven C. Almo, Andrej Sali, Brian K. Shoichet, and Frank M. Raushel [Texas A&M University]

J. Am. Chem. Soc., **135**, 795–803, 2013.

Of the over 22 million protein sequences in the nonredundant TrEMBL database, fewer than 1% have experimentally confirmed functions. Structure-based methods have been used to predict enzyme activities from experimentally determined structures; however, for the vast majority of proteins, no such structures are available. Here, homology models of a functionally uncharacterized amidohydrolase from Agrobacterium radiobacter K84 (Arad3529) were computed on the basis of a remote template structure. . The protein backbone of two loops near the active site was remodeled, resulting in four distinct active site conformations.

Identification of Novel Amino Acid Derived CCK-2R Antagonists As Potential Antiulcer Agent: Homology Modeling, Design, Synthesis, and Pharmacology

Amit K. Gupta, Kanika Varshney, Neetu Singh, Vaibhav Mishra, Mridula Saxena, Gautam Palit, and Anil K. Saxena[CSIR−Central Drug Research Institute]

J.Chem. Infor. and Mod. **53**, 176–187, 2013.

The present study revisited the three-dimensional (3D) homology model of CCK-2R using human A_{2a} adenosine receptor and the resolved NMR based structure of the third extracellular loop of the CCK-2R as templates. Further in order to identify novel antiulcer agents, rational designing have been performed utilizing the substructure of a well-known CCK-2R antagonist benzotript as a lead molecule and submitted to the combined docking and simulation studies. This led to the understanding of the essential structure requirement as well as variation of binding mode among conformational isomers of small molecule CCK-2R antagonists.

Ligand Docking

MolShaCS: A free and open source tool for ligand similarity identification based on Gaussian descriptors

Luis Antônio C. Vaz de Lima, Alessandro S. Nascimento [Universidade Federal do ABC]

Europ. Jou. Med. Chem., **59**, 296-303, 2013.

Molecular similarity evaluation is an important step in most drug development strategies, since molecular similarity is usually related to functional similarity. Here, we developed a method based on the Gaussian description of molecular shape and charge distribution for molecular similarity identification. The method was evaluated using the Directory of Useful Decoys (DUD) and a retrospective test. Enrichment factors computed for DUD targets showed that the proposed method performs very well in recognizing molecules with similar physicochemical properties and dissimilar topologies, reaching an average AUC of 0.63 and enrichment factor of 10 at 0.5% of decoys.

Ligand Docking (Cont'd)

Asymmetric Ligand Binding Facilitates Conformational Transitions in Pentameric Ligand-Gated Ion Channels

David Mowrey, Mary Hongying Cheng, Lu Tian Liu, Dan Willenbring, Xinghua Lu, Troy Wymore, Yan Xu, and Pei Tang [Pittsburgh Supercomputing Center]

J. Am. Chem. Soc., 135**, 2172–2180, 2013.**

A!

The anesthetic propofol inhibits the currents of the homopentameric ligand-gated ion channel GLIC, yet the crystal structure of GLIC with five propofol molecules bound symmetrically shows an open-channel conformation. To address this dilemma and determine if the symmetry of propofol binding sites affects the channel conformational transition, we performed a total of 1.5 μs of molecular dynamics simulations for different GLIC systems with propofol occupancies of 0, 1, 2, 3, and 5. GLIC without propofol binding or with five propofol molecules bound symmetrically, showed similar channel conformation and hydration status over multiple replicates of 100-ns simulations.

Molecular modeling to investigate the binding of Congo red toward GNNQQNY protofibril and in silico virtual screening for the identification of new aggregation inhibitors

Jian-Hua Zhao, Hsuan-Liang Liu, Pavadai Elumalai, Wei-Hsi Chen [National Taipei University of Technology], Lee-Chung Men, Kung-Tien Liu

J. Mol.Mod., **19,** 151-162, 2013.

Understanding the nature of the recognition between amyloid protofibrils and dye molecules at the molecular level is essential to improving instructive guides for designing novel molecular probes or new inhibitors. However, the atomic details of the binding between dyes and amyloid fibrils are still not fully understood. Here, molecular docking, consensus scoring, molecular dynamics, and molecular mechanics Poisson-Boltzmann surface area analyses were integrated to investigate the binding between Congo red (CR) and the GNNQQNY protofibril from yeast prion protein Sup35 and to further evaluate their binding stabilities and affinities.

FINDSITE^{comb}: A Threading/Structure-Based, Proteomic-Scale Virtual Ligand Screening Approach

Hongyi Zhou and Jeffrey Skolnick [Georgia Institute of Technology]

J.Chem. Infor. and Mod. **53**, 230–240, 2013.

Virtual ligand screening is an integral part of the modern drug discovery process. Traditional ligand-based, virtual screening approaches are fast but require a set of structurally diverse ligands known to bind to the target. Traditional structure-based approaches require high-resolution target protein structures and are computationally demanding. In contrast, the recently developed threading/structure-based FINDSITE-based approaches have the advantage that they are as fast as traditional ligand-based approaches and yet overcome the limitations of traditional ligand- or structure-based approaches.

Conformational Dynamics of the FMN-Binding Reductase Domain of Monooxygenase P450BM-3

Rajni Verma, Ulrich Schwaneberg, and Danilo Roccatano [Jacobs University Bremen]

J. Chem. Theor. and Comp, **9**, 96–105, 2013.

In the cytochrome P450BM-3, the flavin mononucleotide (FMN) binding domain is an intermediate electron donor between the flavin adenine dinucleotide (FAD) binding domain and the HEME domain. Experimental evidence has shown that different redox states of FMN cofactor were found to induce conformational changes in the FMN domain. Herein, molecular dynamics (MD) simulation is used to gain insight into the latter phenomenon at the atomistic level.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 39, January 2013.

1-12 **Docking and MD study of histamine H4R based on the crystal structure of H1R,** Zhiwei Feng, Tingjun Hou, Youyong Li [Soochow University]

See Applications / Homology Modeling.

13-22 **Structural analysis of the inhibition of APRIL by TACI and BCMA through molecular dynamics simulations,** Maite González-Mendióroz, Ana Belén Álvarez-Vázquez, Jaime Rubio-Martinez [University of Barcelona]

See Applications / Ligand Binding.

23-28 **Theoretical studies on the common catalytic mechanism of transketolase by using simplified models,** Xiang Sheng, Yongjun Liu [Shandong University], Chengbu Liu

See Applications / Enzyme Catalysis.

29-38 **Modeling the zing finger protein SmZF1 from Schistosoma mansoni: Insights into DNA binding and gene regulation,** Mainá Bitar, Marcela Gonçalves Drummond, Mauricio Garcia Souza Costa, Francisco Pereira Lobo, Carlos Eduardo Calzavara-Silva, Paulo Mascarello Bisch, Carlos Renato Machado, Andréa Mara Macedo, Raymond J. Pierce, Glória Regina Franco [Universidade Federal de Minas Gerais]

See Applications / Protein-Nucleic acids.

39-49 **Softened electrostatic molecular potentials,** Emili Besalú [University of Girona], Ramon Carbó-Dorca

Electrostatic molecular potentials (EMPs) are studied from two points of view. First, a softened EMP (SEMP) approach is proposed, consisting in the substitution of a positive point charge as the entity with which an electronic density function (DF) interacts electrostatically to generate a classical EMP for a Gaussian charge distribution.

50-60 **A homology modeling study toward the understanding of three-dimensional structure and putative pharmacological profile of the G-protein coupled receptor GPR55,** Orgil Elbegdorj, Richard B. Westkaemper, Yan Zhang [Virginia Commonwealth University]

See Applications / Homology Modeling.

61-64 **Study of hydrophobic properties of biologically active open analogues of flavonoids,** Veronika Opletalová, Petr Kastner, Marta Kučerová-Chlupáčová, Karel Palát [Charles University in Prague]

Hydrophobicity can either be determined experimentally or predicted by means of commercially available programs. In the studies concerning biological activities of pyrazine analogues of chalcones, 3-(2-hydroxyphenyl)-1-(pyrazin-2-yl)prop-2-en-1-ones were more potent than the corresponding 3-(4-hydroxyphenyl)-1-(pyrazin-2-yl)prop-2-en-1-ones.

65-70 **Homology modeling and virtual screening approaches to identify potent inhibitors of slingshot phosphatase 1,** Hwangseo Park [Sejong University], So Ya Park, Seong Eon Ryu

See Applications / Homology Modeling.

71-78 **Association of nicotinic acid with a poly(amidoamine) dendrimer studied by molecular dynamics simulations,** Julio Caballero [Universidad de Talca], Horacio Poblete, Cristell Navarro, Jans H. Alzate-Morales

See Applications / Ligand Binding.

79-86 **An in silico approach to evaluate the polyspecificity of methionyl-tRNA synthetases,** Saravanan Prabhu Nadarajan, Sam Mathew, Kanagavel Deepankumar, Hyungdon Yun [Yeungnam University]

See Applications / Enzyme Catalysis.

87-97 **Isolation and in silico evaluation of antidiabetic molecules of Cynodon dactylon (L.),** Hasthi V. Annapurna, Babu Apoorva, Natesan Ravichandran, Kallur Purushothaman Arun, Pemaiah Brindha, Sethuraman Swaminathan, Mahadevan Vijayalakshmi, Arumugam Nagarajan [PSG College of Pharmacy, Peelamedu]

See Applications / Medicinal Chemmistry and Drug Design.

98-107 **Virtual screening for alpha7 nicotinic acetylcholine receptor for treatment of Alzheimer's disease,** Shi-Gao Chen, Ruo-Xu Gu, Hao Dai, Dong-Qing Wei [Shanghai Jiao Tong University]

See Applications / Medicinal Chemmistry and Drug Design.

108-117 **A structural and functional model for human bone sialoprotein,** Kevin Vincent, Marcus C. Durrant [Northumbria University]

See Applications / Homology Modeling.

118-125 **Parameterization of the proline analogue Aze (azetidine-2-carboxylic acid) for molecular dynamics simulations and evaluation of its effect on homo-pentapeptide conformations,** Kyrylo Bessonov, Kenrick A. Vassall, George Harauz [University of Guelph]

See Applications / Protein Dynamics.

Journal of Computational Chemistry, 34 (3), January 2013.

163–174 **Binding structures of tri-N-acetyl-β-glucosamine in hen egg white lysozyme using molecular dynamics with a polarizable force field**, Yang Zhong and Sandeep Patel [University of Delaware]

See Applications / Ligand Binding.

175–186 **$BaTiO_3$-based nanolayers and nanotubes: First-principles calculations**, Robert A. Evarestov [St. Petersburg State University], Andrei V. Bandura and Dmitrii D. Kuruch

See Applications / Carbon Nanotubes.

187–197 **Partial atomic charges and their impact on the free energy of solvation**, Joakim P. M. Jämbeck [Stockholm University], Francesca Mocci, Alexander P. Lyubartsev and Aatto Laaksonen

Free energies of solvation (ΔG) in water and n-octanol have been computed for common drug molecules by molecular dynamics simulations with an additive fixed-charge force field.

198–205 **Rotamer decomposition and protein dynamics: Efficiently analyzing dihedral populations from molecular dynamics**, Hiroshi Watanabe, Marcus Elstner and Thomas Steinbrecher [Inst. Phys. Chem.]

See Applications / Protein Dynamics.

206–219 **Accurate integration over atomic regions bounded by zero-flux surfaces**, Pavel M. Polestshuk [Moscow State University]

The approach for the integration over a region covered by zero-flux surface is described. This approach based on the surface triangulation technique is efficiently realized in a newly developed program TWOE. The elaborated method is tested on several atomic properties including the source function.

220–233 **Global and local indices for characterizing biomolecular flexibility and rigidity**, Christopher Pfleger, Sebastian Radestock, Elena Schmidt and Holger Gohlke [Heinrich-Heine-University]

Understanding flexibility and rigidity characteristics of biomolecules is a prerequisite for understanding biomolecular structural stability and function. Computational methods have been implemented that directly characterize biomolecular flexibility and rigidity by constraint network analysis. We present concise definitions of these indices, analyze the relation between, and the scope and limitations of them, and compare their informative value.

234–244 **Exploring the energy landscapes of flexible molecular loops using higher-dimensional continuation**, Josep M. Porta [UPC-CSIC] and Léonard Jaillet

The conformational space of a flexible molecular loop includes the set of conformations fulfilling the geometric loop-closure constraints and its energy landscape can be seen as a scalar field defined on this implicit set. This article describes these tools and applies them to obtain full descriptions of the energy landscapes of short molecular loops that, otherwise, can only be partially explored, mainly via sampling.

245–255 **Lattice microbes: High-performance stochastic simulation method for the reaction-diffusion master equation**, Elijah Roberts, John E. Stone and Zaida Luthey-Schulten [University of Illinois at Urbana-Champaign]

See Applications / Bioinformatics.

Journal of Computational Chemistry, 34 (4), February 2013.

259–274 **Relations frequency hypermatrices in mutual, conditional and joint entropy-based information indices**, Stephen J. Barigye, Yovani Marrero-Ponce [Universidad Central "Martha Abreu" de Las Villas], Yoan Martínez-López, Francisco Torrens, Luis Manuel Artiles-Martínez, Ricardo W. Pino-Urias and Oscar Martínez-Santiago

Graph-theoretic matrix representations constitute the most popular and significant source of topological molecular descriptors (MDs). Recently, we have introduced a novel matrix representation, named the duplex relations frequency matrix, **F**, derived from the generalization of an incidence matrix whose row entries are connected subgraphs of a given molecular graph **G**. In this report, an extension of **F** is presented, introducing for the first time the concept of a hypermatrix in graph-theoretic chemistry.

275–283 **New basis sets for the evaluation of interaction-induced electric properties in hydrogen-bonded complexes**, Angelika Baranowska-Łączkowska [Kazimierz Wielki University], Berta Fernández and Robert Zaleśny

Interaction-induced static electric properties, that is, dipole moment, polarizability, and first hyperpolarizability, of the CO—$(HF)_n$ and N_2—$(HF)_n$, n = 1–9 hydrogen-bonded complexes are evaluated within the finite field approach using the Hartree–Fock, density functional theory, Møller–Plesset second-order perturbation theory, and coupled cluster methods, and the LPol-n (n = ds, dl, fs, fl) basis sets.

284–293 **Comparison of two simulation methods to compute solvation free energies and partition coefficients**, Li Yang, Alauddin Ahmed and Stanley I. Sandler [University of Delaware]

See Methodology / Free Energy Perturbations.

294–304 **Theoretical description of dihydrogen/hydride and trihydride molybdocene complexes: An insight from static and molecular dynamics simulations**, Łukasz Piękoś and Mariusz Paweł Mitoraj [Jagiellonian University]

In this study ab initio Car–Parrinello molecular dynamics simulations, extended transition state (ETS)-natural orbitals for chemical valence (NOCV) and QTAIM bonding analyses, were performed to characterize the ansa-bridged molybdocene complexes $[(C_5H_4)_2XMe_2MoH_3]^+$ for X = C, Si, Ge, Sn, Pb, and nonbridged $Cp_2MoH_3^+$ system.

305–310 **Electric field assisted oxygen removal from the basal plane of the graphitic material**, Hongguang Liu and Jin Yong Lee [Sungkyunkwan University]

We provide a novel strategy to eliminate the epoxy group from the basal plane of graphene platelets. Given that the current reduction methods are unsatisfactory to clean the epoxides or sometimes cause undesirable structure deformations, the proposed strategy restores the original hexagonal carbon network without creating other new defects.

311–318 **A nonredundant structure dataset for benchmarking protein-RNA computational docking**, Sheng-You Huang and Xiaoqin Zou [University of Missouri]

See Applications / Protein-Nucleic acids.

Journal of Computational Chemistry, 34 (5), February 2013.

337–345 **Accurate Ab initio potential energy surface and vibration-rotation energy levels of hydrogen peroxide**, Paweł Małyszek and Jacek Koput [Adam Mickiewicz University]

The accurate ground-state potential energy surface of hydrogen peroxide, H_2O_2, has been determined from ab initio calculations using the coupled-cluster approach in conjunction with the correlation-consistent basis sets up to septuple-zeta quality.

346–354 **Accurate dynamical structure factors from ab initio lattice dynamics: The case of crystalline silicon**, Alessandro Erba [Università di Torino], Matteo Ferrabone, Roberto Orlando and Roberto Dovesi

A fully ab initio technique is discussed for the determination of dynamical X-ray structure factors (XSFs) of crystalline materials, which is based on a standard Debye–Waller (DW) harmonic lattice dynamical approach with all-electron atom-centered basis sets, periodic boundary conditions, and one-electron Hamiltonians.

355–359 **Esters flash point prediction using artificial neural networks**, Gonzalo Astray, Juan F. Gálvez, Juan C. Mejuto [University of Vigo], Oscar A. Moldes and Iago Montoya

In this article, an artificial neural network to predict the flash point of 95 esters was implemented. Four variables were used for its development. A neural network with 4-5-8-5-1 topology was encountered to gain the best agreement of the experimental results with those predicted (square correlation coefficient (R^2) and root mean square error were 0.99 and 5.46 K for the training phase and 0.96 and 13.02 K for the testing set).

360–365 **Molecular rectification in triangularly shaped graphene nanoribbons**, Hongmei Liu, Hongbo Wang, Jianwei Zhao [Nanjing University] and Manabu Kiguchi

We present a theoretical study of electron transport in tailored zigzag graphene nanoribbons (ZGNRs) with triangular structure using density functional theory together with the nonequilibrium Green's function formalism. We find significant rectification with a favorite electron transfer direction from the vertex to the right edge.

Journal of Molecular Modeling, 19 (1), January 2013.

1-32 **Optimization of parameters for semiempirical methods VI: more modifications to the NDDO approximations and re-optimization of parameters,** James J. P. Stewart [Stewart Computational Chemistry]

See Methodology / Potentilas and Parameters.

33-48 **Theoretical investigations on the structure, density, thermodynamic and performance properties of amino-, methyl-, nitroso- and nitrotriazolones,** P. Ravi [University of Hyderabad], Bonige K. Babu, Suyra P. Tewari

We have studied herein the effect of position and the number of -NO, $-NO_2$, $-NH_2$ and $-CH_3$ groups on the structure, stability, impact sensitivity, density, thermodynamic and detonation properties of triazolones by performing density functional theory calculations at the B3LYP/aug-cc-pVDZ level.

49-55 **Density functional theory study on the reaction mechanism of synthesizing 1,3-dimethyl-2-imidazolidinone by urea method,** Shujuan Yao, Huayong Chen [South China University of Technology], Shu Jiang, Xin Shao, Shouxin Cui

We report a first-principles density functional theory investigation on tailoring the fundamental reaction mechanism of synthesizing 1,3-dimethyl-2-imidazolidinone (DMI) through the urea method with water serving as both solvent and catalyst. The nucleophilic cyclization reaction is implemented by two ammonia removal steps.

57-64 **Theoretical studies on the crystal structure, thermodynamic properties, detonation performance and thermal stability of cage-tetranitrotetraazabicyclooctane as a novel high energy density compound,** Guo-zheng Zhao, Ming Lu [Nanjing University of Science & Technology]

The B3LYP/6-31G (d) method of density functional theory (DFT) was used to study molecular geometry, electronic structure, infrared spectrum (IR) and thermodynamic properties. The heat of formation (HOF) and calculated density were estimated to evaluate the detonation properties using Kamlet–Jacobs equations.

65-71 **Rectifying behavior of charge transfer complexes of tetrakis(dimethylamino)ethene with acceptor molecules: a theoretical study,** Serguei Fomine [Universidad Nacional Autónoma de México]

The effect of electric field induced electron transfer on the rectification properties of molecular rectifiers based on charge transfer complexes of tetrakis(dimethylamino)ethane (TDAE) with acceptor molecules was explored.

73-82 **MD simulation of self-diffusion and structure in some n-alkanes over a wide temperature range at high pressures,** Huajie Feng, Wei Gao, Jingjing Nie, Jing Wang, Xiaojuan Chen, Liuping Chen [Sun Yat-sen University, Guangzhou], Xin Liu, Hans-Dietrich Lüdemann, Zhenfan Sun

Self-diffusion and structural properties of n-alkanes have been studied by molecular dynamics simulation in the temperature range between the melting pressure curve and 600 K at pressures up to 300 MPa.

83-95 **A DFT study on the mechanisms for the cycloaddition reactions between 1−aza-2-azoniaallene cations and acetylenes,** Jing-mei Wang, Zhi-ming Li [Fudan University], Quan-rui Wang, Feng-gang Tao

The mechanisms of cycloaddition reactions between 1-aza-2-azoniaallene cations **1** and acetylenes **2** have been investigated using the global electrophilicity and nucleophilicity of the corresponding reactants as global reactivity indexes defined within the conceptual density functional theory.

97-107 **Electric field effect on the zigzag (6,0) single-wall BC_2N nanotube for use in nano-electronic circuits,** Mohammad T. Baei [Islamic Azad University], Ali Ahmadi Peyghan, Masoumeh Moghimi, Saeede Hashemian

See Applications / Carbon Nanotubes.

109-118 **Characterization of the structures and dynamics of phosphoric acid doped benzimidazole mixtures: a molecular dynamics study,** Minal More, Swagata Pahari, Sudip Roy, Arun Venkatnathan [Indian Institute of Science Education and Research]

Benzimidazole-based polymer membranes like poly(2,5-benzimidazole) (ABPBI) doped with phosphoric acid (PA) are electrolytes that exhibit high proton conductivity in fuel cells at elevated temperatures. The benzimidazole (BI) moiety is an important constituent of these membranes, so the present work was performed in order to achieve a molecular understanding of the BI–PA interactions in the presence of varying levels of the PA dopant, using classical molecular dynamics (MD) simulations.

119-130 **Structure-based design of nitrogen-linked macrocyclic kinase inhibitors leading to the clinical candidate SB1317/TG02, a potent inhibitor of cyclin dependant kinases (CDKs), Janus kinase 2 (JAK2), and Fms-like tyrosine kinase-3 (FLT3),** Anders Poulsen [S*BIO Pte Ltd], Anthony William, Stéphanie Blanchard, Harish Nagaraj, Meredith Williams, Haishan Wang, Angeline Lee, Eric Sun, Ee-Ling Teo, Evelyn Tan, Kee Chuan Goh, Brian Dymock

See Applications / Medicinal Chemmistry and Drug Design.

131-138 **Computational investigation on the new high energy density material of aluminum enriched 1, 1-diamino-2, 2-dinitroethylene,** Liang Bian [Chinese Academy of Sciences], Yuanjie Shu, Jinbao Xu, Lei Wang

Aluminum enriched 1, 1-diamino-2, 2-dinitroethylene (Al-FOX-7) crystal, as a new high energy density material (HEDM), was designed and investigated using grand canonical monte carlo (GCMC), NVT+NPT-molecular dynamics (MD) and GGA-PBE-density functional theory (DFT) methods.

139-149 **Theoretical design study on photophysical property on oligomers based on spirobifluorene and carbazole-triphenylamine for PLED applications,** Xiao-Hua Xie, Wei Shen, Rong-Xing He, Ming Li [Southwest University]

The photophysical properties of five blue light-emitting polymers based on spirobifluorene applied in polymer light-emitting diodes (PLED) materials have been studied by quantum chemistry.

289-298 **Modeling the structure and proton transfer pathways of the mutant His-107-Tyr of human carbonic anhydrase II,** Puspita Halder, Srabani Taraphder [Indian Institute of Technology, Kharagpur]

See Applications / Enzyme Catalysis.

299-304 **Theoretical study of the triangular bonding complex formed by carbon tetrabromide, a halide, and a solvent molecule in the gas phase,** Xiao Ran Zhao, Yu Jie Wu, Juan Han, Qian Jin Shen, Wei Jun Jin [Beijing Normal University, Beijing]

MP2(full)/aug-cc-pVDZ(-PP) computations predict that new triangular bonding complexes $CBr_4 \cdots X^- \cdots H\text{-}C$(where X^- is a halide and H–C refers to a protic solvent molecule) consist of one halogen bond and two hydrogen bonds in the gas phase. Carbon tetrabromide acts as the donor in the halogen bond, while it acts as an acceptor in the hydrogen bond.

305-314 **Periodic density functional theory study of the high-pressure behavior of energetic crystalline 1,4-dinitrofurazano[3, 4-b]piperazine,** Wentao Wang, Weihua Zhu [Nanjing University of Science and Technology], Jinshan Li, Bibo Cheng, Heming Xiao

A detailed study of the structural, electronic, and optical absorption properties of crystalline 1,4-dinitrofurazano[3,4-b]piperazine (DNFP) under hydrostatic pressures of 0–100 GPa was performed using periodic density functional theory.

315-320 **Theoretical study of the decomposition of ethyl and ethyl 3-phenyl glycidate,** Daniela Josa, Angeles Peña-Gallego [Universidade de Santiago de Compostela], Jesús Rodríguez-Otero, Enrique M. Cabaleiro-Lago

The mechanism of the decomposition of ethyl and ethyl 3-phenyl glycidate in gas phase was studied by density functional theory (DFT) and MP2 methods.

321-328 **A density functional theory analysis for the adsorption of the amine group on graphene and boron nitride nanosheets,** Ernesto Chigo Anota [Benemérita Universidad Autónoma de Puebla], Alejandro Rodríguez Juárez, Miguel Castro, Heriberto Hernández Cocoletzi

In this paper first principles total energy calculations to study the adsorption of amine group (NH_2) on graphene (G) and boron nitride (hBN) nanosheets are developed; the density functional theory, within the local density approximation and Perdew-Wang functional was employed.

329-336 **Ab initio study of weakly bound halogen complexes: RX···PH_3,** Herbert C. Georg, Eudes E. Fileti, Thaciana Malaspina [Universidade Federal de São Paulo]

Ab initio calculations were employed to study the role of ipso carbon hybridization in halogenated compounds RX (R = methyl, phenyl, acetyl, H and X = F, Cl, Br and I) and its interaction with a phosphorus atom, as occurs in the halogen bonded complex type RX···PH_3. The analysis was performed using ab initio MP2, MP4 and CCSD(T) methods.

Journal of Molecular Modeling, 19 (2), February 2013.

485-496 **Molecular and structural insight into plasmodium falciparum RIO2 kinase,** Devendra K. Chouhan, Ashoke Sharon, Chandralata Bal [Birla Institute of Technology, Mesra]

See Applications / Enzyme Catalysis.

497-509 **Computational study of EGFR inhibition: molecular dynamics studies on the active and inactive protein conformations,** Napat Songtawee, M. Paul Gleeson, Kiattawee Choowongkomon [Kasetsart University]

See Applications / Protein Confirmational Analysis.

511-519 **A B3LYP and MP2(full) theoretical investigation into the strength of the C–NO_2 bond upon the formation of the intermolecular hydrogen-bonding interaction between HF and the nitro group of nitrotriazole or its methyl derivatives,** Bao-Hui Li, Wen-jing Shi [The Third Hospital of Shanxi Medical University], Fu-de Ren, Yong Wang

The changes of bond dissociation energy (BDE) in the C–NO_2 bond and nitro group charge upon the formation of the intermolecular hydrogen-bonding interaction between HF and the nitro group of 14 kinds of nitrotriazoles or methyl derivatives were investigated using the B3LYP and MP2(full) methods with the 6-311++G**, 6-311++G(2df,2p) and aug-cc-pVTZ basis sets.

521-528 **Molecular dynamics simulations reveal structural instability of human trypsin inhibitor upon D50E and Y54H mutations,** Wanwimon Mokmak, Surasak Chunsrivirot, Anunchai Assawamakin, Kiattawee Choowongkomon, Sissades Tongsima [National Center for Genetic Engineering and Biotechnology, 113 Thailand Science Park]

See Applications / Protein Structure Analysis.

529-538 **Correlation between substituent constants and hyperpolarizabilities for di-substituted trans-azobenzenes,** Tsung-Yi Lin, Ajay Chaudhari, Shyi-Long Lee [National Chung Cheng University]

Nonlinear optical properties of a series of disubstituted trans-azobenzenes were studied. The structures were fully optimized by B3LYP/6-31+G* and both static polarizabilities and hyperpolarizabilities were then calculated by the derivative method.

539-549 **`Principal component and clustering analysis on molecular dynamics data of the ribosomal L11·23S subdomain,** Antje Wolf, Karl N. Kirschner [Fraunhofer-Institute for Algorithms and Scientific Computing (SCAI)]

See Methodology / Molecular Dynamics.

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1. APPLICATIONS

1.1. *Small Molecules*

Organic Solvents

Convergence of Sampling Kirkwood–Buff Integrals of Aqueous Solutions with Molecular Dynamics Simulations

Pritam Ganguly and Nico F. A. van der Vegt [Technische Universität Darmstadt]

J. Chem. Theor. and Comp, **9**, 1347–1355, 2013.

We discuss two methods for calculating Kirkwood–Buff integrals (KBIs) of aqueous cosolvent solutions from molecular simulations. The first method is based on computing running integrals over radial distribution functions obtained from NVT or NpT simulations. The second, more recent method, originally introduced by Schnell et al. (*J. Phys. Chem. B***2011**, *115*, 10911), obtains the KBIs from direct analysis of particle number fluctuations in small, open subvolumes embedded in a larger reservoir as provided by the NVT (NpT) simulation cell.

Surface Tension of Organic Liquids Using the OPLS/AA Force Field

Rafael A. Zubillaga, Ariana Labastida, Bibiana Cruz, Juan Carlos Martínez, Enrique Sánchez, and José Alejandre [Universidad Autónoma de la Ciudad de México]

J. Chem. Theor. and Comp, **9**, 1611–1615, 2013.

Molecular dynamics simulations are performed to obtain the surface tension of 61 organic liquids using the OPLS/AA (all-atom optimized potential for liquid simulations). The force field parameters are the same as those recently used (Caleman et al. *J. Chem. Theory Comput.***2012**, *8*, 61) to determine several thermodynamic properties of 146 organic liquids. The correct evaluation of surface tension using slab simulations of liquids requires one to properly take into account the long-range interactions (Trukhymchuk and Alejandre *J. Chem. Phys.***1999**, *111*, 8510).

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Medicinal Chemistry and Drug Design

Rational design, synthesis and QSAR study of vasorelaxant active 3-pyridinecarbonitriles incorporating 1H-benzimidazol-2-yl function

Zeinab M. Nofal, Aladdin M. Srour, Wafaa I. El-Eraky, Dalia O. Saleh, Adel S. Girgis [National Research Centre, Dokki]

Europ. Jou. Med. Chem., **63**, 14-21, 2013.

A variety of 2-alkoxy-4-aryl-6-(1*H*-benzimidazol-2-yl)-3-pyridinecarbonitriles **4a**–**r** were prepared via either regioselective reaction of 3-aryl-1-(1*H*-benzimidazol-2-yl)-2-propen-1-ones **3** with malononitrile or ylidenemalononitriles **6** with 2-acetyl-1*H*-benzimidazoles **1** in the presence of sodium alkoxide in the corresponding alcohol. All the synthesized compounds showed significant vasodilation properties using isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride standard technique.

A!

Identification of potential bivalent inhibitors from natural compounds for acetylcholinesterase through *in silico* screening using multiple pharmacophores

V. Lakshmi, V. Santhosh Kannan, R. Boopathy[Bharathiar University]

J. Mol.Graph. and Mod., **40,** 72-79, 2013.

The symptomatic cure observed in the treatment of Alzheimer's disease (AD) by FDA approved drugs could possibly be due to their specificity against the active site of acetylcholinesterase (AChE) and not by targeting its pathogenicity. The AD pathogenicity involved in AChE protein is mainly due to amyloid beta peptide aggregation, which is triggered specifically by peripheral anionic site (PAS) of AChE. In the present study, a workflow has been developed for the identification and prioritization of potential compounds that could interact not only with the catalytic site but also with the PAS of AChE. To elucidate the essential structural elements of such inhibitors, pharmacophore models were constructed using PHASE, based on a set of fifteen best known AChE inhibitors.

Chemosensitizing acridones: In vitro calmodulin dependent *c*AMP phosphodiesterase inhibition, docking, pharmacophore modeling and 3D QSAR studies

V.V.S. Rajendra Prasad, G. Deepa Reddy, D. Appaji, G.J. Peters ,Y.C. Mayur [Dr. Bhanuben Nanavati College of Pharmacy]

J. Mol.Graph. and Mod., **40,** 116–124, 2013.

Calmodulin inhibitors have proved to play a significant role in sensitizing MDR cancer cells by interfering with cellular drug accumulation. The present investigation focuses on the evaluation of in vitro inhibitory efficacy of chloro acridones against calmodulin dependent *c*AMP phosphodiesterase (PDE1c). Moreover, molecular docking of acridones was performed with PDE1c in order to identify the possible protein ligand interactions and results thus obtained were compared with in vitro data. . In addition an efficient pharmacophore model was developed from a set of 38 chemosensitizing acridones effective against doxorubicin resistant (HL-60/DX) cancer cell lines.

Medicinal Chemistry and Drug Design (Cont'd)

2D- and 3D-QSAR studies of a series of benzopyranes and benzopyrano[3,4b][1,4]-oxazines as inhibitors of the multidrug transporter P-glycoprotein

Ishrat Jabeen, Penpun Wetwitayaklung, Peter Chiba, Manuel Pastor, Gerhard F. Ecker[University of Vienna,]

J. Comp. Aided Mol. Des.,**27**, 161-171, 2013.

The ATP-binding cassette efflux transporter P-glycoprotein (P-gp) is notorious for contributing to multidrug resistance in antitumor therapy. Due to its expression in many blood-organ barriers, it also influences the pharmacokinetics of drugs and drug candidates and is involved in drug/drug- and drug/nutrient interactions. A series of Benzopyranes and Benzopyrano[3,4b][1,4]oxazines have been synthesized and pharmacologically tested for their ability to inhibit P-gp mediated daunomycin efflux. Both quantitative structure–activity relationship (QSAR) models using simple physicochemical and novel GRID-independent molecular descriptors (GRIND) were established to shed light on the structural requirements for high P-gp inhibitory activity.

Psoralen Derivatives as Inhibitors of NF-κB/DNA Interaction: Synthesis, Molecular Modeling, 3D-QSAR, and Biological Evaluation

Giovanni Marzaro, Adriano Guiotto, Monica Borgatti, Alessia Finotti, Roberto Gambari, Giulia Breveglieri, and Adriana Chilin[Università degli Studi di Padova]

J.Med.Chem., **56,** 1830-1842, 2013.

Some new psoralen derivatives were synthesized and evaluated as inhibitors of NF-κB/DNA interaction, with the aim to investigate the structural determinants required to inhibit this interaction. Starting from molecular docking studies, several possible protein binding sites were proposed and several three-dimensional quantitative structure–activity relationship (3D-QSAR) models were built using the docked poses of **29** (the most active psoralen in the series) as templates for alignment of the inhibitors. The selected best model was validated through the prediction of the activity of 17 novel compounds.

Interaction of dihydrofolate reductase and aminoglycoside adenyltransferase enzyme from *Klebsiella pneumoniae* multidrug resistant strain DF12SA with clindamycin: a molecular modelling and docking study

Shailesh K. Shahi, Vinay K. Singh, Ashok Kumar[Banaras Hindu University Varanasi]

J. Mol.Mod., **19,** 973-983, 2013.

Klebsiella pneumoniae strain DF12SA (HQ114261) was isolated from diabetic foot wounds. The strain showed resistance against ampicillin, kanamycin, gentamicin, streptomycin, spectinomycin, trimethoprim, tetracycline, meropenem, amikacin, piperacillin/tazobactam, augmentin, co-trimoxazole, carbapenems, penicillins and cefoperazone, and was sensitive to clindamycin. Molecular characterization of the multidrug-resistance phenotype revealed the presence of a class 1 integron containing two genes, a dihydrofolate reductase (*DHFR*) (PF00186), which confers resistance to trimethoprim; and aminoglycoside adenyltransferase (*AadA*) (PF01909), which confers resistance to streptomycin and spectinomycin. A class 1 integron in *K. pneumoniae* containing these two genes was present in eight (18.18 %) out of 44 different diabetic foot ulcer (DFU) patients.

Medicinal Chemistry and Drug Design (Cont'd)

Drug permeability prediction using PMF method

Fancui Meng, Weiren Xu [Tianjin Key Laboratory of Molecular Design and Drug Discovery]

J. Mol.Mod., **19,** 991-997, 2013.

permeability makes a drug unsuitable for further development. The permeability may be estimated as the free energy change that the drug should overcome through crossing membrane. In this paper the drug permeability was simulated using molecular dynamics method and the potential energy profile was calculated with potential of mean force (PMF) method. The membrane was simulated using DPPC bilayer and three drugs with different permeability were Drug permeability determines the oral availability of drugs via cellular membranes. Poor tested.

In vitro inhibitory profile of NDGA against AChE and its in silico structural modifications based on ADME profile

Chandran Remya, Kalarickal Vijayan Dileep, Ignatius Tintu[Kannur University]

J. Mol.Mod., **19,** 1179-1194, 2013.

Acetylcholinesterase (AChE) inhibitors are currently in focus for the pharmacotherapy of Alzheimer's disease (AD). These inhibitors increase the level of acetylcholine in the brain and facilitate cholinergic neurotransmission. AChE inhibitors such as rivastigmine, galantamine, physostigmine and huperzine are obtained from plants, indicating that plants can serve as a potential source for novel AChE inhibitors. We have performed a virtual screening of diverse natural products with distinct chemical structure against AChE. NDGA was one among the top scored compounds and was selected for enzyme kinetic studies.

***In silico* identification of novel inhibitors against *Plasmodium falciparum* dihydroorate dehydrogenase**

Abdul Wadood[University of Karachi]

J. Mol.Graph. and Mod., **40,** 44-47, 2013.

Plasmodium falciparum causes the most fatal form of malaria and accounts for over 1 million deaths annually, yet currently used drug therapies are compromised by resistance. The malaria parasite cannot salvage pyrimidines and relies on *de novo* biosynthesis for survival. The enzyme dihydrooratate dehydrogenase (DHODH), a mitochondrial flavoenzyme, catalyzes the rate-limiting step of this pathway and is therefore an attractive anti-malarial chemotherapeutic target. In an effort to design new and potential anti-malarials, structure-based pharmacophore mapping, molecular docking, binding energy calculations and binding affinity predictions were employed in a virtual screening strategy to design new and potent.

Medicinal Chemistry and Drug Design (Cont'd)

Interaction between shrimp and white spot syndrome virus through PmRab7-VP28 complex: an insight using simulation and docking studies

Arunima Kumar Verma, Shipra Gupta, Sharad Verma, Abha Mishra, N. S. Nagpure[Indian Council of Agricultural Research]

J. Mol.Mod., **19,** 1285-1294,2013.

A!

White spot disease is a devastating disease of shrimp *Penaeus monodon* in which the shrimp receptor protein PmRab7 interacts with viral envelop protein VP28 to form PmRab7–VP28 complex, which causes initiation of the disease. The molecular mechanism implicated in the disease, the dynamic behavior of proteins as well as interaction between both the biological counterparts that crafts a micro-environment feasible for entry of virus into the shrimp is still unknown. In the present study, we applied molecular modeling (MM), molecular dynamics (MD) and docking to compute surface mapping of infective amino acid residues between interacting proteins.

New pockets in dengue virus 2 surface identified by molecular dynamics simulation

Carlos A. Fuzo,Léo Degrève[Universidade de São Paulo]

J. Mol.Mod., **19,** 1369-1377, 2013.

One of the factors limiting the search of new compounds based on the structure of target proteins involved in diseases is the limited amount of target structural information. In the case of dengue, the discovery of pockets in the crystallographic structure of the E protein has contributed to the search for lead compounds aimed at interfering in conformational transitions involved in the pH-dependent fusion process. In the present work, an arrangement of three ectodomain portions of the E protein present on the surface of the mature dengue virus was studied through long all-atom molecular dynamics simulations with explicit solvent.

Synthesis and evaluation of resveratrol derivatives as new chemical entities for cancer

Chaitanya Mulakayala, B. Babajan, P. Madhusudana, C.M. Anuradha, Raja Mohan Rao, Ravi Prakash Nune, Sunil Kumar Manna, Naveen Mulakayala, Chitta Suresh Kumar[Sri Krishandevaraya University]

J. Mol.Graph. and Mod., **41,** 43-54, 2013.

Resveratrol has been shown to be active in inhibiting multistage carcinogenesis. The potential use of resveratrol in cancer chemoprevention or chemotherapy settings has been hindered by its short half-life and low bioavailability. Considering the above remarks, using resveratrol as a prototype, we have synthesized two derivatives of resveratrol. Their activity was evaluated using in-vitro and in-silico analysis. Biological evaluation of resveratrol analogues on U937 cells had shown that two synthesized analogues of resveratrol had higher rates of inhibition than the parental molecule at 10 μM concentration.

Medicinal Chemistry and Drug Design (Cont'd)

Structural basis of femtomolar inhibitors for acetylcholinesterase subtype selectivity: Insights from computational simulations

Xiao-Lei Zhu, Ning-Xi Yu, Ge-Fei Hao, Wen-Chao Yang, Guang-Fu Yang[Central China Normal University]

J. Mol.Graph. and Mod., **41,** 55-60, 2013.

Acetylcholinesterase (AChE) is a key enzyme of the cholinergic nervous system. More than one gene encodes the synaptic AChE target. As the most potent known AChE inhibitor, the *syn*1-TZ2PA6 isomer was recently shown to have higher affinity as a reversible organic inhibitor of acetylcholinesterase1 (AChE1) than the *anti*1-TZ2PA6 isomer. Opposite selectivity has been shown for acetylcholinesterase2 (AChE2). In an attempt to understand the selectivity of the *syn*1-TZ2PA6 and *anti*1-TZ2PA6 isomers for AChE1 and AChE2, six molecular dynamics (MD) simulations were carried out with mouse AChE (mAChE, type of AChE1), Torpedo californica AChE (*Tc*AChE, type of AChE1), and Drosophila melanogaster AChE (*Dm*AChE, type of AChE2) bound with *syn*1-TZ2PA6 and *anti*1-TZ2PA6 isomers

Quantitative Structure-Activity Relations

QSAR studies of sulfamate and sulfamide inhibitors targeting human carbonic anhydrase isozymes I, II, IX and XII

Laszlo Tarko [Romanian Academy, Bucharest], Claudiu T. Supuran

Bioorg. and Med.Chem., **21**, 1404-1409, 2013.

The last version of the PRECLAV algorithm was used to investigate a series of sulfamate/sulfamide carbonic anhydrase (CA, EC 4.2.1.1) inhibitors. PRECLAV allows identification of outliers for lead hopping, significant molecular fragments and similarity computation of a calibration set vs. a prediction set of compounds, from the viewpoint of computed QSAR. In the current study the database included 65 sulfamates and sulfamides as calibration set and 51 not yet synthesized sulfamates and sulfamides as prediction set. The dependent property was inhibitory activity for human (h) CA isozymes I, II, IX and XII.

Chemometric QSAR modeling and in silico design of carbonic anhydrase inhibition of a coral secretory isoform by sulfonamide

Shalini Singh [Bareilly College], Claudiu T. Supuran

Bioorg. and Med.Chem., **21**, 1495-1502, 2013.

Scleractinian coral stylophora pistillata carbonic anhydrase (STPCA) enzyme is a secreted isoform, plays a direct role in bio-mineralization. Sulfonamides, including some clinically used derivatives are the most important class of STPCA inhibitors. In order to search for efficient STPCA inhibitors molecules, the present work deals with quantitative structure–activity relationship (QSAR) studies of a series of 36 bioactive molecules. A heuristic algorithm selects the best multiple linear regression (MLR) equation showed the correlation between the observed values and the calculated values of activity is very good (N = 36, Se = 0.1683, r^2 = 0.9158, F = 54.3809, = 0.8569).

Quantitative Structure Activity Relations (Cont'd)

3D-QSAR studies of azaoxoisoaporphine, oxoaporphine, and oxoisoaporphine derivatives as anti-AChE and anti-AD agents by the CoMFA method

Yan-Ping Li, Xiang Weng, Fang-Xian Ning, Jie-Bin Ou, Jin-Qiang Hou, Hai-Bin Luo[Sun Yat-sen University], Ding Li, Zhi-Shu Huang, Shi-Liang Huang, Lian-Quan Gu

J. Mol.Graph. and Mod., **41,** 61-67, 2013.

In the present study, a series of novel azaoxoisoaporphine derivatives were reported and their inhibitory activities toward acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), and Aβ aggregation were evaluated. The new compounds remained high inhibitory potency on Aβ aggregation, with inhibitory activity from 29.42% to 89.63% at a concentration of 10 μM, but had no action on AChE or BuChE, which was very different from our previously reported oxoaporphine and oxoisoaporphine derivatives. By 3D-QSAR studies, we constructed a reliable CoMFA model ($q^2 = 0.856$ and $r^2 = 0.986$) based on the inhibitory activities toward AChE and discovered key information on structure and anti-AChE activities among the azaoxoisoaporphine, oxoaporphine, and oxoisoaporphine derivatives

Carbon Nanoparticles

Polymerization of miniature fullerenes in the cavity of nanotubes

O. E. Glukhova, A. S. Kolesnikova, M. M. Slepchenkov [Department of Physics]

J. Mol.Mod., **19,** 985-990, 2013.

The polymerization of four fullerenes C_{28} in the cavity of closed single-walled carbon nanotube C_{740} was investigated. It was shown that the formation of the oligomer of four C_{28} fullerenes is observed at the pressure of 37.73 GPa, which is created by means of the charged fullerene C_{60}. Fullerene C_{60} moves under the influence of an external electric field.

Simple benzene derivatives adsorption on defective single-walled carbon nanotubes: a first-principles van der Waals density functional study

Masoud Darvish Ganji, Maryam Mohseni, Anahita Bakhshandeh[Islamic Azad University,]

J. Mol.Mod., **19,** 1059-1067, 2013.

We have investigated the interaction between open-ended zig-zag single-walled carbon nanotube (SWCNT) and a few benzene derivatives using the first-principles van der Waals density functional (vdW-DF) method, involving full geometry optimization. Such sp^2-like materials are typically investigated using conventional DFT methods, which significantly underestimate non-local dispersion forces (vdW interactions), therefore affecting interactions between respected molecules.

Interactions between Multiwall Carbon Nanotubes and Poly(diallyl dimethylammonium) Chloride: Effect of the Presence of a Surfactant

Prabhsharan Kaur, Mun-Sik Shin, Anjali Joshi, Namarta Kaur, Neha Sharma, Jin-Soo Park, and S. S. Sekhon[Guru Nanak Dev University]

J. Phys. Chem. B., **117**, 3161–3166, 2013**.**

The interactions between multiwall carbon nanotubes (MWCNTs) and poly(diallyl dimethylammonium) chloride (PDDA) have been studied in the presence of different ionic and nonionic surfactants, such as sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB), Tween 20, 40, 60, and 80, and Triton X-100. On the basis of scanning electron microscopy (SEM) results, the MWCNT/PDDA sample treated with Triton X-100 has been observed to show good dispersion of nanotubes.

Carbon Nanoparticles (Cont'd)

Mechanism of Electrolyte-Induced Brightening in Single-Wall Carbon Nanotubes

Juan G. Duque, Laura Oudjedi, Jared J. Crochet, Sergei Tretiak, Brahim Lounis,

J. Am. Chem. Soc., 2013, **135**, pp 3379–3382

While addition of electrolyte to sodium dodecyl sulfate suspensions of single-wall carbon nanotubes has been demonstrated to result in significant brightening of the nanotube photoluminescence (PL), the brightening mechanism has remained unresolved. Here, we probe this mechanism using time-resolved PL decay measurements. We find that PL decay times increase by a factor of 2 on addition of CsCl as the electrolyte.

Site-Specific Immobilization of Single-Walled Carbon Nanotubes onto Single and One-Dimensional DNA Origami

Anshuman Mangalum, Masudur Rahman, and Michael L. Norton

J. Am. Chem. Soc., 2013, **135**, 2451–2454

Development of a simple and efficient methodology to control the placement, spacing, and alignment of single-walled carbon nanotubes (SWCNTs) is essential for nanotechnology device application. Building on the growing understanding that the strong π–π interaction between the bases of single-stranded DNA (ssDNA) and CNTs is sufficient not only to drive CNT solubility in water but also to stabilize individual nanotubes against clustering in aqueous solution, a new motif for functionalizing DNA origami (DO) with CNTs is demonstrated. CNTs solubilized via wrapping with ssDNA react with DO constructs displaying linear arrays of ssDNA, leading to immobilization of the CNTs onto the DO scaffold. This study demonstrates the immobilization of ssDNA-wrapped CNTs at specific positions on single DO constructs.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

The prediction of palmitoylation site locations using a multiple feature extraction method

Shao-Ping Shi Xing-Yu Sun, Jian-Ding QiuSheng-Bao Suo, Xiang Chen, Shu-Yun Huang, Ru-Ping Liang[Nanchang University]

J. Mol.Graph. and Mod., **40,** 125-130, 2013.

As an extremely important and ubiquitous post-translational lipid modification, palmitoylation plays a significant role in a variety of biological and physiological processes. Unlike other lipid modifications, protein palmitoylation and depalmitoylation are highly dynamic and can regulate both protein function and localization. The dynamic nature of palmitoylation is poorly understood because of the limitations in current assay methods. The in vivo or in vitro experimental identification of palmitoylation sites is both time consuming and expensive. . In this work, a new computational method, WAP-Palm, combining multiple feature extraction, has been developed to predict the palmitoylation sites of proteins

Bioinformatics and Cheminformatics (Cont'd)

Algorithms of GPU-enabled reactive force field (ReaxFF) molecular dynamics

Mo Zheng[Graduate University of Chinese Academy of Sciences] ,Xiaoxia Li, Li Guo

J. Mol.Graph. and Mod., **41,** 1-11, 2013.

Reactive force field (ReaxFF), a recent and novel bond order potential, allows for reactive molecular dynamics (ReaxFF MD) simulations for modeling larger and more complex molecular systems involving chemical reactions when compared with computation intensive quantum mechanical methods. However, ReaxFF MD can be approximately 10–50 times slower than classical MD due to its explicit modeling of bond forming and breaking, the dynamic charge equilibration at each time-step, and its one order smaller time-step than the classical MD. In this paper, we present the algorithms of GMD-Reax, the first GPU enabled ReaxFF MD program with significantly improved performance surpassing CPU implementations on desktop workstations.

MagiC: Software Package for Multiscale Modeling

Alexander Mirzoev and Alexander P. Lyubartsev [Stockholm University]

J. Chem. Theor. and Comp, **9**, 1512–1520, 2013.

A!

We present software package MagiC, which is designed to perform systematic structure-based coarse graining of molecular models. The effective pairwise potentials between coarse-grained sites of low-resolution molecular models are constructed to reproduce structural distribution functions obtained from the modeling of the system in a high resolution (atomistic) description. The software supports coarse-grained tabulated intramolecular bond and angle interactions, as well as tabulated nonbonded interactions between different site types in the coarse-grained system, with the treatment of long-range electrostatic forces by the Ewald summation.

Comparative or Homology Modeling

Prediction of Long Loops with Embedded Secondary Structure Using the Protein Local Optimization Program

Edward B. Miller, Colleen S. Murrett, Kai Zhu, Suwen Zhao, Dahlia A. Goldfeld, Joseph H. Bylund, and Richard A. Friesner[Columbia Universit]

J. Chem. Theor. and Comp, **9**, 1846–1864, 2013.

Robust homology modeling to atomic-level accuracy requires in the general case successful prediction of protein loops containing small segments of secondary structure. Further, as loop prediction advances to success with larger loops, the exclusion of loops containing secondary structure becomes awkward. Here, we extend the applicability of the Protein Local Optimization Program (PLOP) to loops up to 17 residues in length that contain either helical or hairpin segments. In general, PLOP hierarchically samples conformational space and ranks candidate loops with a high-quality molecular mechanics force field.

Comparative or Homology Modeling (Cont'd)

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J. Chem. Theor. and Comp, **9**, 1846–1864, 2013.

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In silico characterization of a novel β-1,3-glucanase gene from *Bacillus amyloliquefaciens*—a bacterial endophyte of *Hevea brasiliensis* antagonistic to *Phytophthora meadii*

Amith Abraham, Sunilkumar Puthenpurackal Narayanan [Mahatma Gandhi University]

J. Mol.Mod., **19,** 999-1007, 2013.

We report the molecular characterization of β-1,3-glucanase-producing *Bacillus amyloliquefaciens*—an endophyte of *Hevea brasiliensis* antagonistic to *Phytophthora meadii*. After cloning and sequencing, the β-1,3-glucanase gene was found to be 747 bp in length. A homology model of the β-1,3-glucanase protein was built from the amino acid sequence obtained upon translation of the gene. The target β-1,3-glucanase protein and the template protein, endo β-1,3-1,4-glucanase protein (PDB ID: 3o5s), were found to share 94 % sequence identity and to have similar secondary and tertiary structures.

Protein Structure Analysis

The role of glycine residues at the C-terminal peptide segment in antinociceptive activity: a molecular dynamics simulation

Yong-Shan Zhao, Rong Zhang, Yang Xu, Yong Cui, Yan-Feng Liu, Yong-Bo Song, Hong-Xing Zhang, Jing-Hai Zhang [Shenyang Pharmaceutical University]

J. Mol.Mod., **19,** 1295-1299, 2013.

Elucidating structural determinants in the functional regions of toxins can provide useful knowledge for designing novel analgesic peptides. Glycine residues at the C-terminal region of the neurotoxin BmK AGP-SYPU2 from the scorpion *Buthus martensii* Karsch (BmK) have been shown to be crucial to its analgesic activity. We performed three MD simulations: one on the native structure and the other two on mutants of that structure.

Supramolecular Organization of Heptapyrenotide Oligomers—An in Depth Investigation by Molecular Dynamics Simulations

Fabio Simona, Alina L. Nussbaumer, Robert Häner, and Michele Cascella [University of Bern]

J. Phys. Chem. B., **117**, 2576–2585, 2013**.**

We present a molecular modeling study based on ab initio and classical molecular dynamics calculations, for the investigation of the tridimensional structure and supramolecular assembly formation of heptapyrenotide oligomers in water solution. Our calculations show that free oligomers self-assemble in helical structures characterized by an inner core formed by π-stacked pyrene units, and external grooves formed by the linker moieties

Protein Structure Analysis (Cont'd)

Structural features of cholesteryl ester transfer protein: A molecular dynamics simulation study

Dongsheng Lei, Xing Zhang, Shengbo Jiang, Zhaodi Cai, Matthew J. Rames, Lei Zhang, Gang Ren and Shengli Zhang[Lawrence Berkeley National Laboratory]

Proteins: Stru. Fun. & Bioinf., **81**, 415–425, 2013

A!

Cholesteryl ester transfer protein (CETP) mediates the net transfer of cholesteryl esters (CEs) from atheroprotective high-density lipoproteins (HDLs) to atherogenic low-density lipoproteins (LDLs) or very-low-density lipoproteins (VLDLs). Inhibition of CETP raises HDL cholesterol (good cholesterol) levels and reduces LDL cholesterol (bad cholesterol) levels, making it a promising drug target for the prevention and treatment of coronary heart disease. Although the crystal structure of CETP has been determined, the molecular mechanism mediating CEs transfer is still unknown, even the structural features of CETP in a physiological environment remain elusive. We performed molecular dynamics simulations to explore the structural features of CETP in an aqueous solution.

Protein Dynamics

pK_a Determination of Histidine Residues in α-Conotoxin MII Peptides by ^1H NMR and Constant pH Molecular Dynamics Simulation

Owen M. McDougal[Boise State University], David M. Granum, Mark Swartz, Conrad Rohleder, and C. Mark Maupin

J. Phys. Chem. B., **117**, 2653–2661, 2013**.**

α-Conotoxin MII (α-CTxMII) is a potent and selective peptide antagonist of neuronal nicotinic acetylcholine receptors (nAChR's). Studies have shown that His9 and His12 are significant determinants of toxin binding affinity for nAChR, while Glu11 may dictate differential toxin affinity between nAChR isoforms. The protonation state of these histidine residues and therefore the charge on the α-CTx may contribute to the observed differences in binding affinity and selectivity. In this study, we assess the pH dependence of the protonation state of His9 and His12 by ^1H NMR spectroscopy and constant pH molecular dynamics (CpHMD) in α-CTxMII, α-CTxMII[E11A], and the triple mutant, α-CTxMII[N5R:E11A:H12K].

ViewMotions Rainbow: A new method to illustrate molecular motions in proteins

Gregory M. Cockrell, Evan R. Kantrowitz[Merkert Chemistry Center, Chestnut Hill]

J. Mol.Graph. and Mod., **40,** 48-53, 2013.

The biological functions of many enzymes are often coupled with significant conformational changes. The end states of these conformational changes can often be determined by X-ray crystallography. These X-ray structures are snapshots of the two extreme conformations in which the macromolecule exists, but the dynamic movements between the states are not easily visualized in a two-dimensional illustration. Here we have developed a new method to visualize macromolecular motions called a ViewMotions Rainbow diagram. These diagrams show the initial and final states overlaid along with approximately 30 intermediate structures calculated by linear interpolation of the backbone coordinates of the initial and final states

Protein Dynamics (Cont'd)

Impact of deglycosylation and thermal stress on conformational stability of a full length murine igG2a monoclonal antibody: Observations from molecular dynamics simulations

Xiaoling Wang, Sandeep Kumar [BioTherapeutics Pharmaceutical Sciences Pfizer Inc], Patrick M. Buck and Satish K. Singh

Proteins: Stru. Fun. & Bioinf., **81**, 443–460, 2013.

With the rise of antibody based therapeutics as successful medicines, there is an emerging need to understand the fundamental antibody conformational dynamics and its implications towards stability of these medicines. Both deglycosylation and thermal stress have been shown to cause conformational destabilization and aggregation in monoclonal antibodies. Here, we study instabilities caused by deglycosylation and by elevated temperature (400 K) by performing molecular dynamic simulations on a full length murine IgG2a mAb whose crystal structure is available in the Protein Data bank

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The interactions and recognition of cyclic peptide mimetics of Tat with HIV-1 TAR RNA: a molecular dynamics simulation study

Chun Hua Li, Zhi Cheng Zuo, Ji Guo Su, Xian Jin Xu & Cun Xin Wang

J. Biomol. Stru. and Dyn., **31**,(3) 276-287,2013.

The interaction of HIV-1 trans-activator protein Tat with its cognate trans-activation response element (TAR) RNA is critical for viral transcription and replication. Therefore, it has long been considered as an attractive target for the development of antiviral compounds. Recently, the conformationally constrained cyclic peptide mimetics of Tat have been tested to be a promising family of lead peptides. Here, we focused on two representative cyclic peptides termed as L-22 and KP-Z-41, both of which exhibit excellent inhibitory potency against Tat and TAR interaction.

Computer modeling on the tautomerization of sulbactam intermediate in SHV-1 β-lactamases: E166A mutant vs. wild type

Rui Li, Yeng-Tseng Wang, Cheng-Lung Chen[Liaocheng University]

J. Mol.Graph. and Mod., **40,** 131–139, 2013.

A!

We present a theoretical study for the tautomerization of sulbactam intermediates in different SHV-1 β-lactamases: E166A and wild-type (WT). Molecular dynamics (MD) simulations were employed and hydrogen bonds network around active site was found different between the WT and E166A acyl-enzymes. In E166A, Asn170 restricts the C5—C6 bond rotation, thus stabilizes the dihedral angle N4—C5—C6—C7 of imine to a trans conformation. The DFT calculations (B3LYP/6-31+G* and B3LYP/6-31++G**) were performed on tautomerization reactions.

Toward an understanding of the sequence and structural basis of allosteric proteins

Xiaobai Li ,Yingyi Chen ,Shaoyong Lu ,Zhimin Huang ,Xinyi Liu ,Qi Wang ,Ting Shi ' Jian Zhang [Shanghai JiaoTong University]

J. Mol.Graph. and Mod., **40,** 30-39, 2013.

Allostery is the most efficient means of regulating protein functions, ranging from the control of metabolic mechanisms to signal transduction pathways. Although allosteric regulation has been recognized for half a century, our knowledge is limited to the characteristics of allosteric proteins and the structural coupling of allosteric sites and modulators. In this paper, we present a comprehensive analysis of allosteric proteins that provides insight into the foundation of allosteric interactions by revealing a series of common features in the allosteric proteins. Allosteric proteins mainly appear in transferases, and phosphorylation is the most common type of modification found in allosteric proteins.

Protein Dynamics (Cont'd)

Water PMF for predicting the properties of water molecules in protein binding site

Mingyue Zheng[1,†], Yanlian Li[2,†], Bing Xiong[2,*], Hualiang Jiang[1], Jingkang Shen[2,*] [Shanghai Institute of Materia Medica,]

J. Comp. Chem., **34**,583–592, 2013.

Water is an important component in living systems and deserves better understanding in chemistry and biology. However, due to the difficulty of investigating the water functions in protein structures, it is usually ignored in computational modeling, especially in the field of computer-aided drug design. Here, using the potential of mean forces (PMFs) approach, we constructed a water PMF (wPMF) based on 3946 non-redundant high resolution crystal structures. The extracted wPMF potential was first used to investigate the structure pattern of water and analyze the residue hydrophilicity.

Prediction of Hydrodynamic and Other Solution Properties of Partially Disordered Proteins with a Simple, Coarse-Grained Model

D. Amorós, A. Ortega, and J. García de la Torre [Universidad de Murcia]

J. Chem. Theor. and Comp, **9**, 1678–1685, 2013.

The possibility of validating structures of intrinsically disordered proteins against solution properties is a goal that would be most helpful in the understanding of their function. We have devised a scheme for the prediction of solution properties of partially disordered proteins that comprise one or more ordered domains, along with flexible tails or linkers. A very simple, coarse-grained, residue-level model, which is easily parametrized using available structural information, along with previously developed tools for the simulation of solution conformation and dynamics, allows the prediction of properties like sedimentation coefficients, relaxation times, and X-ray or neutron scattering.

$(Ala)_4$-X-$(Ala)_4$ as a model system for the optimization of the χ_1 and χ_2 amino acid side-chain dihedral empirical force field parameters

jihyun Shim[1], Xiao Zhu[1], Robert B. Best[2], Alexander D. MacKerell Jr.[1] [University of Maryland]

J. Comp. Chem., **34**, 593–603, 2013.

Amino acid side-chain fluctuations play an essential role in the structure and function of proteins. Accordingly, in theoretical studies of proteins, it is important to have an accurate description of their conformational properties. Recently, new side-chain torsion parameters were introduced into the CHARMM and Amber additive force fields and evaluated based on the conformational properties of the individual side-chains using protein simulations in explicit solvent.

A!

Hydrophobic Interaction Drives Surface-Assisted Epitaxial Assembly of Amyloid-like Peptides

Seung-gu Kang, Tien Huynh, Zhen Xia, Yi Zhang, Haiping Fang, Guanghong Wei, and Ruhong Zhou

J. Am. Chem. Soc., 2013, **135**, 3150–3157

The molecular mechanism of epitaxial fibril formation has been investigated for GAV-9 (NH_3^+-VGGAVVAGV-$CONH_2$), an amyloid-like peptide extracted from a consensus sequence of amyloidogenic proteins, which assembles with very different morphologies, "upright" on mica and "flat" on the highly oriented pyrolytic graphite (HOPG). Our all-atom MD simulations reveal that the strong electrostatic interaction induces the "upright" conformation on mica, whereas the hydrophobic interaction favors the "flat" conformation on HOPG. We also show that the epitaxial pattern on mica is ensured by the lattice matching between the anisotropic binding sites of the basal substrate and the molecular dimension of GAV-9, accompanied with a long-range order of well-defined β-strands

Protein Dynamics (Cont'd)

Chiral Sum Frequency Generation for In Situ Probing Proton Exchange in Antiparallel β-Sheets at Interfaces

Li Fu, Dequan Xiao, Zhuguang Wang, Victor S. Batista, and Elsa C. Y. Yan

J. Am. Chem. Soc., 2013, 135 (9), pp 3592–3598

Studying hydrogen/deuterium (H/D) exchange in proteins can provide valuable insight on protein structure and dynamics. Several techniques are available for probing H/D exchange in the bulk solution, including NMR, mass spectroscopy, and Fourier transform infrared spectroscopy. However, probing H/D exchange at interfaces is challenging because it requires surface-selective methods. Here, we introduce the combination of in situ chiral sum frequency generation (cSFG) spectroscopy and ab initio simulations of cSFG spectra as a powerful methodology to probe the dynamics of H/D exchange at interfaces.

Free Energy Calculations

Role of tyrosine hot-spot residues at the interface of colicin E9 and immunity protein 9: A comparative free energy simulation study

Manuel P. Luitz and Martin Zacharias[Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **81**, 461–468, 2013.

The endonuclease activity of the bacterial colicin 9 enzyme is controlled by the specific and high-affinity binding of immunity protein 9 (Im9). Molecular dynamics simulation studies in explicit solvent were used to investigate the free energy change associated with the mutation of two hot-spot interface residues [tyrosine (Tyr): Tyr54 and Tyr55] of Im9 to Ala. In addition, the effect of several other mutations (Leu33Ala, Leu52Ala, Val34Ala, Val37Ala, Ser48Ala, and Ile53Ala) with smaller influence on binding affinity was also studied.

Ligand Binding/Docking

Quantifying Changes in Intrinsic Molecular Motion Using Support Vector Machines

Ralph E. Leighty and Sameer Varma [University of South Florida]

J. Chem. Theor. and Comp, **9**, 868–875, 2013.

The ensemble of three-dimensional (3-D) configurations exhibited by a molecule, that is, its intrinsic motion, can be altered by several environmental factors, and also by the binding of other molecules. Here, we introduce a method based on support vector machines that yields a normalized quantitative estimate for the difference between two ensembles after comparing them directly against one another. While this method can be applied to any molecular system, including nonbiological molecules and crystals, here, we show how it can be applied to identify the specific regions of a paramyxovirus G protein that are affected by the binding of its preferred human receptor, Ephrin B2.

Ligand Binding / Docking (Cont'd)

Investigation of the influence of molecular topology on ligand binding

Rurika Oka[a, b], Ola Engkvist[b], Hongming Chen[b][Lund University]

J. Mol.Graph. and Mod., **40,** 22-29, 2013.

Molecular topology class has previously been put forward as a new concept of describing compound quality and it has been shown that compared to general bioactive compounds, drugs is more similar to natural products and human metabolites in terms of molecular topology class distribution, in which they are enriched with compounds having only one ring system. To further understand how the molecular topology is influencing the drug discovery process, we have investigated the compound potency of different molecular topologies in published chemical patents.

Assessment of new anti-HER2 ligands using combined docking, QM/MM scoring and MD simulation

Marawan Ahmed, Maiada M. Sadek, Rabah A. Serrya, Abdel-Hamid N. Kafafy, Khaled A. Abouzid, Feng Wang[Swinburne University of Technology]

J. Mol.Graph. and Mod., **40,** 91-98, 2013.

In the development of new anti-cancer drugs to tackle the problem of resistance to current chemotherapeutic agents, a new series of anti-HER2 (human epidermal growth factor receptors 2) agents has been synthesized and investigated using different computational methods. Although non-selective, the most active inhibitor in the new series shows higher activity toward HER2 than EGFR. Molecular dynamic simulations of the inhibitor–protein complexes for the two most active compounds from the new series are carried out.

Towards the identification of the binding site of benzimidazoles to β-tubulin of *Trichinella spiralis*: Insights from computational and experimental data

Rodrigo Aguayo-Ortiz ,Oscar Méndez-Lucio ,José L. Medina-Franco ,Rafael Castillo ,Lilián Yépez-Mulia ,Francisco Hernández-Luis ,Alicia Hernández-Campos[a,] [Universidad Nacional Autónoma de México]

J. Mol.Graph. and Mod., **41,** 12-19, 2013.

A!

Benzimidazole-2-carbamate derivatives (BzC) are among the most important broad-spectrum anthelmintic drugs for the treatment of nematode infections. BzC selectively bind to the β-tubulin monomer and inhibit microtubule polymerization. However, the crystallographic structure of the nematode tubulin and the mechanism of action are still unknown. Moreover, the relation between the mechanism of action and the binding site of BzC has not yet been explained accurately. By using the amino acid sequence of *Trichinella spiralis* β-tubulin as a basis and by applying homology modeling techniques, we were able to build a 3D structure of this protein. In order to identify a binding site for BzC, molecular docking and molecular dynamics calculations were carried out with this model.

Insight into the dynamic interaction between different flavonoids and bovine serum albumin using molecular dynamics simulations and free energy calculations

Xiaodi Niu, Xiaohan Gao, Hongsu Wang, Xin Wang, Song Wang[Jilin University,]

J. Mol.Mod., **19,** 1039-1047, 2013.

In this study, the binding of Bovine serum albumin (BSA) with three flavonoids, kaempferol-3-*O*-a-L-rhamnopyranosyl-(1–3)-a-L-rhamnopyranosyl-(1–6)-b-D-galacto- pyranoside (drug 1),kaempfol-7-*O*-rhamnosyl-3-*O*-rutinoside (drug 2)andkaempferide-7-O-(4"-*O*-acetylrhamnosyl)-3-*O*-ruti- noside (drug 3) is investigated by molecular docking, molecular dynamics (MD) simulation, and binding free energy calculation. The free energies are consistent with available experimental results and suggest that the binding site of BSA-drug1 is more stable than those of BSA-drug2 and BSA-drug3.

Ligand Binding / Docking (Cont'd)

Molecular dynamic simulation of mGluR5 amino terminal domain: essential dynamics analysis captures the agonist or antagonist behaviour of ligands

Alessandro Casoni, Francesca Clerici, Alessandro Contini[Università degli Studi di Milano]

J. Mol.Graph. and Mod., **41,** 72-78, 2013.

We describe the application of molecular dynamics followed by principal component analysis to study the inter-domain movements of the ligand binding domain (LBD) of mGluR5 in response to the binding of selected agonists or antagonists. Our results suggest that the method is an attractive alternative to current approaches to predict the agonist-induced or antagonist-blocked LBD responses. The ratio between the eigenvalues of the first and second eigenvectors ($R_{1,2}$) is also proposed as a numerical descriptor for discriminating the ligand behavior as a mGluR5 agonist or antagonist.

Simultaneous Solvent and Counterion Effects on the Absorption Properties of a Model of the Rhodopsin Chromophore

Aurora Muñoz-Losa [Universidad de Extremadura], Ignacio Fdez. Galván, Manuel A. Aguilar, and M. Elena Martín

J. Chem. Theor. and Comp, **9**, 1548–1556, 2013.

The ASEP/MD (averaged solvent electrostatic potential from molecular dynamics) method was employed in studying the environment effects (solvent and counterion) on the absorption spectrum of a model of the 11-*cis*-retinal protonated Schiff base. Experimental studies of the absorption spectra of the rhodopsin chromophore show anomalously large solvent shifts in apolar solvents. In order to clarify their origin, we study the role of the counterion and of the solute–solvent interactions. We compare the absorption spectra in the gas phase, cyclohexane, dichloromethane, and methanol

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Native-Based Simulations of the Binding Interaction Between RAP74 and the Disordered FCP1 Peptide

Sushant Kumar, Scott A. Showalter, and William G. Noid [The Pennsylvania State University]

J. Phys. Chem. B., **117**, 3074–3085, 2013**.**

By dephosphorylating the C-terminal domain (CTD) of RNA polymerase II (Pol II), the Transcription Factor IIF (TFIIF)-associating CTD phosphatase (FCP1) performs an essential function in recycling Pol II for subsequent rounds of transcription. The interaction between FCP1 and TFIIF is mediated by the disordered C-terminal tail of FCP1, which folds to form an α-helix upon binding the RAP74 subunit of TFIIF. The present work reports a structure-based simulation study of this interaction between the folded winged-helix domain of RAP74 and the disordered C-terminal tail of FCP1.

Molecular dynamics and free energy studies of chirality specificity effects on aminobenzo[a]quinolizine inhibitors binding to DPP-IV

Cui Wei, Liang Desheng, Gao Jian, Luo Fang, Geng Lingling [Graduate University of the Chinese Academy of Sciences]

J. Mol.Mod., **19,** 1167-1177, 2013.

The aminobenzo[a]quinolizines were investigated as a novel class of DPP-IV inhibitors. The stereochemistry of this class plays an important role in the bioactivity. In this study, the mechanisms of how different configuration of three chiral centers of this class influences the binding affinity were investigated by molecular dynamics simulations, free energy decomposition analysis. The S configuration for chiral center 3* is decisive for isomers to maintain high bioactivity; the chirality effect of chiral center 2* on the binding affinity is largely dependent, while the S configuration for chiral center 2* is preferable to R configuration for the bioactivity gain; the effect of chiral center 11b* on the binding affinity is insignificant.

Ligand Binding / Docking (Cont'd)

StudieS on the binding modes of Lassa nucleoprotein complexed with m7GpppG and dTTP by molecular dynamic simulations and free energy calculations

Liang Li, Dan Li, Hang Chen & Ju-Guang Han

J. Biomol. Stru. and Dyn., **31**,(3) 299-315,2013.

Lassa virus can cause dreadful human hemorrhagic disease, for which there is no effective therapy. A recent study points out that the amino (N)-terminal domain of Lassa virus nucleoprotein (NP) plays an important role in viral RNA synthesis and firstly solved the X-ray crystal structures of NP complexed with the capped Deoxythymidine triphosphate (dTTP) analog, but the binding mode of m7GpppG to the N domain of NP, which is required for viral RNA transcription, has not been studied. In this study, molecular dynamics (MD) simulations have been carried out to investigate the characters of dTTP binding to two forms of NP, i.e. the NP without the C domain and the full-length NP model, using two different force fields, ff03 and ff99SB, respectively.

Enzyme Catalysis

Elucidating the catalytic mechanism of β-secretase (BACE1): A quantum mechanics/molecular mechanics (QM/MM) approach

Arghya Barman, Rajeev Prabhakar [University of Miami]

J. Mol.Graph. and Mod., **40,** 1-9, 2013.

In this QM/MM study, the mechanisms of the hydrolytic cleavage of the Met2-Asp3 and Leu2-Asp3 peptide bonds of the amyloid precursor protein (WT-substrate) and its Swedish mutant (SW) respectively catalyzed by β-secretase (BACE1) have been investigated by explicitly including the electrostatic and steric effects of the protein environment in the calculations. BACE1 catalyzes the rate-determining step in the generation of Alzheimer amyloid beta peptides and is widely acknowledged as a promising therapeutic target. The general acid-base mechanism followed by the enzyme proceeds through the following two steps: (1) formation of the gem-diol intermediate and (2) cleavage of the peptide bond.

Mechanism of the irreversible inhibition of human cyclooxygenase-1 by aspirin as predicted by QM/MM calculations

L. Tóth ,L. Muszbek ,I. Komáromi[University of Debrecen]

J. Mol.Graph. and Mod., **40,** 99–109, 2013.

Acetylsalicylic acid (aspirin) suppresses the generation of prostaglandin H2, which is the precursor of thromboxane A2. Aspirin acts as an acetylating agent in which its acetyl group is covalently attached to a serine residue (S530) in the active site of the cyclooxygenase-1 enzyme. The exact reaction mechanism has not been revealed by experimental methods. In this study the putative structure of human cyclooxygenase-1 was constructed from ovine cyclooxygenase-1 by homology modeling, and the acetylsalicylic acid was docked into the arachidonic acid binding cavity of the enzyme.

Enzyme Catalysis (Cont'd)

Molecular dynamics simulation of PNPLA3 I148M polymorphism reveals reduced substrate access to the catalytic cavity

Yong-Ning Xin, Yuqi Zhao, Zhong-Hua Lin, Xiangjun Jiang, Shi-Ying Xuan [Qingdao Municipal Hospital]and Jingfei Huang

Proteins: Stru. Fun. & Bioinf., **81**, 406–414, 2013.

A!

A missense mutation I148M in PNPLA3 (patatin-like phospholipase domain-containing 3 protein) is significantly correlated with nonalcoholic fatty liver disease (NAFLD). To glean insights into mutation's effect on enzymatic activity, we performed molecular dynamics simulation and flexible docking studies. Our data show that the size of the substrate-access entry site is significantly reduced in mutants, which limits the access of palmitic acid to the catalytic dyad.

Impact of Substrate Protonation and Tautomerization States on Interactions with the Active Site of Arginase I

Shanthi Nagagarajan, Fengtian Xue, and Alexander D. MacKerell, Jr. [University of Maryland,]

J.Chem. Infor. and Mod. **53**, 452–460, 2013.

A!

Human arginase is a binuclear manganese metalloenzyme that participates in the urea cycle. Arginase catalyzes the hydrolysis of l-arginine into l-ornithine and urea and is linked to several disorders such as asthma and cancer. Currently, the protonation and tautomerization state of the substrate when bound to the active site, which contains two manganese ions, is not known. The arginine$^{+/0}$ species, including all possible neutral tautomers, were modeled using an aminoimidazole analog as template. All-atom molecular dynamics simulations were then performed on each of the charged and neutral species.

Probing mechanism of metal catalyzed hydrolysis of Thymidylyl (3′-O, 5′-S) thymidine phosphodiester derivatives

Mahboobeh Rahimian, Shridhar P. Gejji [University of Pune]

J. Mol.Mod., **19,** 1027-1037, 2013.

Hydrolysis of nucleic acids is of fundamental importance in biological sciences. Kinetic and theoretical studies on different substrates wherein the phosphodiester bond combined with alkyl or aryl groups and sugar moiety have been the focus of attention in recent literature. The present work focuses on understanding the mechanism and energetics of alkali metal (Li, Na, and K) catalyzed hydrolysis of phosphodiester bond in modeled substrates including Thymidylyl (3′-O, 5′-S) thymidine phosphodiester (Tp-ST) *(1)*, 3′-Thymidylyl (1-trifluoroethyl) phosphodiester (Tp-OCH_2CF_3) *(2)*, 3′-Thymidylyl (o-cholorophenyl) phosphodiester (Tp-OPh(o-Cl)) *(3)* and 3′-Thymidylyl(p-nitrophenyl) phosphodiester (Tp-OPh(p-NO_2)) *(4)* employing density functional theory

Membrane Proteins and Lipid Peptide Interactions

A Comparison of Coarse-Grained and Continuum Models for Membrane Bending in Lipid Bilayer Fusion Pores

Jejoong Yoo, Meyer B. Jackson, Qiang Cui [University of Wisconsin, Madison]

Biophysical Journal. **104**, 841-852, 2013.

To establish the validity of continuum mechanics models quantitatively for the analysis of membrane remodeling processes, we compare the shape and energies of the membrane fusion pore predicted by coarse-grained (MARTINI) and continuum mechanics models. The results at these distinct levels of resolution give surprisingly consistent descriptions for the shape of the fusion pore, and the deviation between the continuum and coarse-grained models becomes notable only when the radius of curvature approaches the thickness of a monolayer. The combined coarse-grained and continuum analysis confirms the recent prediction of continuum models that the fusion pore is a metastable structure and that its optimal shape is neither toroidal nor catenoidal.

Molecular Dynamics Simulation Analysis of Membrane Defects and Pore Propensity of Hemifusion Diaphragms

Manami Nishizawa, Kazuhisa Nishizawa [Teikyo University School of Medical Technology]

Biophysical Journal. **104**, 1038-1048, 2013.

Membrane fusion often exhibits slow dynamics in electrophysiological experiments, involving prespike foot and fusion pore-flickering, but the structural basis of such phenomena remains unclear. Hemifusion intermediates have been implicated in the early phase of membrane fusion. To elucidate the dynamics of formation of membrane defects and pores within the hemifusion diaphragm (HD), atomistic and coarse-grained models of hemifusion intermediates were constructed using dipalmitoylphosphatidylcholine or dioleoylphosphatidylcholine membranes.

AutoMap: A tool for analyzing protein–ligand recognition using multiple ligand binding modes

Mark Agostino ,Ricardo L. Mancera ,Paul A. Ramsland ,Elizabeth Yuriev[Monash University]

J. Mol.Graph. and Mod., **40,** 80-90, 2013.

Prediction of the protein residues most likely to be involved in ligand recognition is of substantial value in structure-based drug design. Considering multiple ligand binding modes is of potential relevance to studying ligand recognition, but is generally ignored by currently available techniques. AutoMap is a partially automated implementation of our previously developed site mapping procedure. AutoMap determines the hydrogen bonding and van der Waals interactions taking place between a target protein and each pose of a ligand ensemble. It tallies these interactions according to the protein residues with which they occur, then normalizes the tallies and maps these to the surface of the protein.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Structural Modeling of HCV NS3/4A Serine Protease Drug-Resistance Mutations Using End-Point Continuum Solvation and Side-Chain Flexibility Calculations

Hajira Ahmed Hotiana and Muhammad Kamran Haider[Lahore University of Management Sciences]

J.Chem. Infor. and Mod. **53**, 435–451, 2013.

A!

Computational methods of modeling protein–ligand interactions have gained widespread application in modern drug discovery. In continuum solvation-based methods of binding affinity estimation, limited description of solvent environment and protein flexibility is traded for a time scale that fits medicinal chemistry test cycles. The results of this speed-accuracy trade-off have been promising in terms of modeling structure–activity relationships of ligand series against protein targets. We used continuum solvation binding affinity predictions and graph theory-based flexibility calculations to model thirteen drug resistance mutations in HCV NS3/4A serine protease, against three small-molecule inhibitors.

Dynamic Heterogeneous Dielectric Generalized Born (DHDGB): An Implicit Membrane Model with a Dynamically Varying Bilayer Thickness

Afra Panahi and Michael Feig [Michigan State University]

J. Chem. Theor. and Comp, **9**, 1709–1719, 2013.

A!

An extension to the heterogeneous dielectric generalized Born (HDGB) implicit membrane formalism is presented to allow dynamic membrane deformations in response to membrane-inserted biomolecules during molecular dynamic simulations. The flexible membrane is implemented through additional degrees of freedom that represent the membrane deformation at the contact points of a membrane-inserted solute with the membrane. The extra degrees of freedom determine the dielectric and nonpolar solvation free energy profiles that are used to obtain the solvation free energy in the presence of the membrane and are used to calculate membrane deformation free energies according to an elastic membrane model.

How Warfarin's Structural Diversity Influences Its Phospholipid Bilayer Membrane Permeation

Björn C. G. Karlsson [Linnæus University], Gustaf D. Olsson, Ran Friedman, Annika M. Rosengren, Henning Henschel, and Ian A. Nicholls

J. Phys. Chem. B., **117**, 2273–2279, 2013**.**

The role of the structural diversity of the widely used anticoagulant drug warfarin on its distribution in 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) bilayer membranes was investigated using a series of both restrained (umbrella sampling) and unrestrained molecular dynamics simulations. Data collected from unrestrained simulations revealed favorable positions for neutral isomers of warfarin, the open side chain form (OCO), and the cyclic hemiketal (CCO), along the bilayer normal close to the polar headgroup region and even in the relatively distant nonpolar lipid tails.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Protein–Ligand Binding from Distancefield Distances and Hamiltonian Replica Exchange Simulations

Anita de Ruiter and Chris Oostenbrink [University of Natural Resources and Life Sciences (BOKU]

J. Chem. Theor. and Comp, **9**, 883–892, 2013.

The calculation of protein–ligand binding free energies is an important goal in the field of computational chemistry. Applying path-sampling methods for this purpose involves calculating the associated potential of mean force (PMF) and gives insight into the binding free energy along the binding process. DF is a grid-based method in which the shortest distance between the binding site and a ligand is determined avoiding routes that pass through the protein. Combining this reaction coordinate with Hamiltonian replica exchange molecular dynamics (HREMD) allows for the reversible binding of the ligand to the protein.

Efficient Relaxation of Protein–Protein Interfaces by Discrete Molecular Dynamics Simulations

Agusti Emperador, Albert Solernou, Pedro Sfriso, Carles Pons, Josep Lluis Gelpi, Juan Fernandez-Recio, and Modesto Orozco [Facultat de Biologia]

J. Chem. Theor. and Comp, **9**, 1222–1229, 2013.

Protein–protein interactions are responsible for the transfer of information inside the cell and represent one of the most interesting research fields in structural biology. Unfortunately, after decades of intense research, experimental approaches still have difficulties in providing 3D structures for the hundreds of thousands of interactions formed between the different proteins in a living organism. In this work, we present a new approach to treat flexibility in docking by global structural relaxation based on ultrafast discrete molecular dynamics.

Molecular Insight into Affinities of Drugs and Their Metabolites to Lipid Bilayers

Markéta Paloncýová, Karel Berka [Palacký University Olomouc], and Michal Otyepka

J. Phys. Chem. B., **117**, 2403–2410, 2013**.**

The penetration properties of drug-like molecules on human cell membranes are crucial for understanding the metabolism of xenobiotics and overall drug distribution in the human body. Here, we analyze partitioning of substrates of cytochrome P450s (caffeine, chlorzoxazone, coumarin, ibuprofen, and debrisoquine) and their metabolites (paraxanthine, 6-hydroxychlorzoxazone, 7-hydroxycoumarin, 3-hydroxyibuprofen, and 4-hydroxydebrisoquine) on two model membranes: dioleoylphosphatidylcholine (DOPC) and palmitoyloleoylphophatidylglycerol (POPG). We calculated the free energy profiles of these molecules and the distribution coefficients on the model membranes.

How Cholesterol Tilt Modulates the Mechanical Properties of Saturated and Unsaturated Lipid Membranes

George Khelashvili and Daniel Harries[University of Jerusalem]

J. Phys. Chem. B., **117**, 2411–2421, 2013**.**

Although there have been great advances in understanding the effect of cholesterol on various properties of lipid membranes, its mechanistic role in determining the elasticity of bilayers at the molecular level is not fully resolved. Indeed, to date the molecular mechanisms that drive the experimentally detected differences in properties of saturated and unsaturated lipid bilayers that contain cholesterol remain unclear. By quantifying the cholesterol orientational degrees of freedom from atomistic molecular dynamics simulations of mixed lipid-cholesterol membranes, we address this question from the perspective of cholesterol tilt and splay.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Prediction, refinement, and persistency of transmembrane helix dimers in lipid bilayers using implicit and explicit solvent/lipid representations: Microsecond molecular dynamics simulations of ErbB1/B2 and EphA1

Liqun Zhang, Alexander J. Sodt, Richard M. Venable, Richard W. Pastor and Matthias Buck[Case Western Reserve University]

Proteins: Stru. Fun. & Bioinf., **81**, 365–376, 2013.

A!

All-atom simulations are carried out on ErbB1/B2 and EphA1 transmembrane helix dimers in lipid bilayers starting from their solution/DMPC bicelle NMR structures. Over the course of microsecond trajectories, the structures remain in close proximity to the initial configuration and satisfy the majority of experimental tertiary contact restraints. These results further validate CHARMM protein/lipid force fields and simulation protocols on Anton. Separately, dimer conformations are generated using replica exchange in conjunction with an implicit solvent and lipid representation.

Protein Folding

The role of loop closure propensity in the refolding of Rop protein probed by molecular dynamics simulations

Rashmi Tambe Shukla[a], Chetana Baliga[b, 1], Yellamraju U. Sasidhar [Indian Institute of Technology Bombay]

J. Mol.Graph. and Mod., **40,** 10-21, 2013.

Rop protein is a homo-dimer of helix-turn-helix and has relatively slow folding and unfolding rates compared to other dimeric proteins of similar size. Fluorescence studies cited in literature suggest that mutation of turn residues D30-A31 to G30-G31 (Gly_2) increases its folding and unfolding rates considerably. A further increase in number of glycines in the turn region results in decrease of folding rates compared to Gly_2 mutant. To understand the effect of glycine mutation on folding/unfolding rates of Rop and the conformational nature of turn region involved in formation of early folding species, we performed molecular dynamics simulations of turn peptides, ^{25}KLNEL**DA**DEQ^{34} (**DA** peptide), ^{25}KLNELGGDEQ^{34} (**G_2** peptide), ^{25}KLNEL**GGG**DEQ^{35} (**G_3** peptide) and ^{25}KLNEL**GGG**EQ^{34} (**$G_{3'}$** peptide) from Rop at 300 K.

Folding Kinetics and Unfolded State Dynamics of the GB1 Hairpin from Molecular Simulation

David De Sancho, Jeetain Mittal, and Robert B. Best[National Institutes of Health, Bethesda]

J. Chem. Theor. and Comp, **9**, 1743–1753, 2013.

The C-terminal β-hairpin of protein G is a 16-residue peptide that folds in a two-state fashion akin to many larger proteins. However, with an experimental folding time of ~6 μs, it remains a challenging system for all-atom, explicitly solvated, molecular dynamics simulations. Here, we use a large simulation data set (0.7 ms total) of the hairpin at 300 and 350 K to interpret its folding via a master equation approach. We find a separation of over an order of magnitude between the longest and second longest relaxation times, with the slowest relaxation corresponding to folding.

Protein Folding (Cont'd)

Effect of High Exogenous Electric Pulses on Protein Conformation: Myoglobin as a Case Study

Paolo Marracino, Francesca Apollonio, Micaela Liberti, Guglielmo d'Inzeo, and Andrea Amadei[Università di Roma 'Tor Vergat]

J. Phys. Chem. B., **117**, 2273–2279, 2013**.**

Protein folding and unfolding under the effect of exogenous perturbations remains a topic of great interest, further enhanced by recent technological developments in the field of signal generation that allow the use of intense ultrashort electric pulses to directly interact at microscopic level with biological matter. In this paper, we show results from molecular dynamics (MD) simulations of a single myoglobin molecule in water exposed to pulsed and static electric fields, ranging from 10^8 to 10^9 V/m, compared to data with unexposed conditions.

As good as it gets? Folding molecular dynamics simulations of the LytA choline-binding peptide result to an exceptionally accurate model of the peptide structure

Ilias Patmanidis, Nicholas M. Glykos[Democritus University of Thrace]

J. Mol.Graph. and Mod., **41,** 68-71, 2013.

Folding simulations of a choline-binding peptide derived from the *Streptococcus pneumoniae* LytA protein converged to a model of the peptide's folded state structure which is in outstanding agreement with the experimentally-determined structures, reaching values for the root mean squared deviation as low as 0.24 Å for the peptide's backbone atoms and 0.65 Å for all non-hydrogen atoms.

Protein-Nucleic acid Interactions

Regulatory mechanism of the light-activable allosteric switch LOV–TAP for the control of DNA binding: A computer simulation study

Emanuel Peter, Bernhard Dick and Stephan A. Baeurle[University of Regensburg]

Proteins: Stru. Fun. & Bioinf., **81**, 365–376, 2013.

The spatio-temporal control of gene expression is fundamental to elucidate cell proliferation and deregulation phenomena in living systems. Novel approaches based on light-sensitive multiprotein complexes have recently been devised, showing promising perspectives for the noninvasive and reversible modulation of the DNA-transcriptional activity *in vivo*. Here, we elucidate the early stages of the light-induced regulatory mechanism of LOV–TAP at the molecular level, using the noninvasive molecular dynamics simulation technique.

Self-Assembled Nanoscale DNA–Porphyrin Complex for Artificial Light Harvesting

Jakob G. Woller, Jonas K. Hannestad, and Bo Albinsson

J. Am. Chem. Soc., 2013, **135**, 2759–2768

Mimicking green plants' and bacteria's extraordinary ability to absorb a vast number of photons and harness their energy is a longstanding goal in artificial photosynthesis. Resonance energy transfer among donor dyes has been shown to play a crucial role on the overall transfer of energy in the natural systems. Here, we present artificial, self-assembled, light-harvesting complexes consisting of DNA scaffolds, intercalated YO-PRO-1 (YO) donor dyes and a porphyrin acceptor anchored to a lipid bilayer, conceptually mimicking the natural light-harvesting systems.

Nucleic Acids

Influence of 8-Oxoguanosine on the Fine Structure of DNA Studied with Biasing-Potential Replica Exchange Simulations

Mahmut Kara, Martin Zacharias [Technische Universität München]

Biophysical Journal. **104**, 1089-1097, 2013.

Chemical modification or radiation can cause DNA damage, which plays a crucial role for mutagenesis of DNA, carcinogenesis, and aging. DNA damage can also alter the fine structure of DNA that may serve as a recognition signal for DNA repair enzymes. A new, advanced sampling replica-exchange method has been developed to specifically enhance the sampling of conformational substates in duplex DNA during molecular dynamics (MD) simulations. The approach employs specific biasing potentials acting on pairs of pseudodihedral angles of the nucleic acid backbone that are added in the replica simulations to promote transitions of the most common substates of the DNA backbone.

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pH-Dependent Dynamics of Complex RNA Macromolecules

Garrett B. Goh, Jennifer L. Knight, and Charles L. Brooks, III [University of Michigan]

J. Chem. Theor. and Comp, **9**, 935–943, 2013.

A!

The role of pH-dependent protonation equilibrium in modulating RNA dynamics and function is one of the key unanswered questions in RNA biology. Molecular dynamics (MD) simulations can provide insight into the mechanistic roles of protonated nucleotides, but it is only capable of modeling fixed protonation states and requires prior knowledge of the key residue's protonation state. Recently, we developed a framework for constant pH molecular dynamics simulations (CPHMD$^{MS\lambda D}$) of nucleic acids, where the nucleotides' protonation states are modeled as dynamic variables that are coupled to the structural dynamics of the RNA.

Toward Reproducing Sequence Trends in Phosphorus Chemical Shifts for Nucleic Acids by MD/DFT Calculations

Jana Přecechtělová, Markéta L. Munzarová [Masaryk University], Juha Vaara, Jan Novotný, Martin Dračínský, and Vladimír Sklenář

J. Chem. Theor. and Comp, **9**, 1641–1656, 2013.

This work addresses the question of the ability of the molecular dynamics–density functional theory (MD/DFT) approach to reproduce sequence trend in ^{31}P chemical shifts (δP) in the backbone of nucleic acids. δP for $[d(CGCGAATTCGCG)]_2$, a canonical B-DNA, have been computed using density functional theory calculations on model compounds with geometries cut out of snapshots of classical molecular dynamics (MD) simulations. The values of ^{31}P chemical shifts for two distinct B-DNA subfamilies BI and BII, δP/BI and δP/BII, have been determined as averages over the BI and BII subparts of the MD trajectory.

Nucleic Acids (Cont'd)

RNA/Peptide Binding Driven by Electrostatics—Insight from Bidirectional Pulling Simulations

Trang N. Do, Paolo Carloni, Gabriele Varani, and Giovanni Bussi[International School for Advanced Studies]

J. Chem. Theor. and Comp, **9**, 1720–1730, 2013.

RNA/protein interactions play crucial roles in controlling gene expression. They are becoming important targets for pharmaceutical applications. Due to RNA flexibility and to the strength of electrostatic interactions, standard docking methods are insufficient. We here present a computational method which allows studying the binding of RNA molecules and charged peptides with atomistic, explicit-solvent molecular dynamics. In our method, a suitable estimate of the electrostatic interaction is used as an order parameter (collective variable) which is then accelerated using bidirectional pulling simulations.

Hole Wave Functions and Transport with Deazaadenines Replacing Adenines in DNA

Alexander J. Breindel, Rachel E. Stuart, William J. Bock, David N. Stelter, Shane M. Kravec, and Esther M. Conwell [University of Rochester]

J. Phys. Chem. B., **117**, 3086–3090, 2013**.**

Transport of a hole along the base stack of DNA is relatively facile for a series of adenines (As) paired with thymines (Ts) or for a series of guanines (Gs) paired with cytosines (Cs). However, the speed at which a hole was found to travel was much too small to make useful semiconductor-type devices. Quite recently it was found that replacing one of the electronegative nitrogens (N3 or N7) with a carbon and a hydrogen, thus turning A into deazaadenine, increased the hole speed in what was A/T by a factor 30. To study the effect of the substitution we have carried out simulations for the wave function of a hole on an A/T oligomer with As modified by replacing N3 or N7, or both, with C–H's.

RNA 3D Structure Prediction by Using a Coarse-Grained Model and Experimental Data

Zhen Xia, David R. Bell, Yue Shi, and Pengyu Ren[University of Texas at Austin]

J. Phys. Chem. B., **117**, 3135–3144, 2013**.**

RNAs form complex secondary and three-dimensional structures, and their biological functions highly rely on their structures and dynamics. Here we developed a general coarse-grained framework for RNA 3D structure prediction. A new, hybrid coarse-grained model that explicitly describes the electrostatics and hydrogen-bond interactions has been constructed based on experimental structural statistics. With the simulated annealing simulation protocol, several RNAs of less than 30-nt were folded to within 4.0 Å of the native structures.

Theoretical study on the binding mechanism between N6-methyladenine and natural DNA bases

Qi-Xia Song, Zhen-Dong Ding, Jian-Hua Liu, Yan Li[The Key Laboratory of Food Colloids and Biotechnology]

J. Mol.Mod., **19,** 1089-1098, 2013.

N6-methyladenine (m^6A) is a rare base naturally occurring in DNA. It is different from the base adenine due to its $N\text{-}CH_3$. Therefore, the base not only pairs with thymine, but also with other DNA bases (cytosine, adenine and guanine). In this work, Møller-Plesset second-order (MP2) method has been used to investigate the binding mechanism between m^6A and natural DNA bases in gas phase and in aqueous solution. The results show that $N\text{-}CH_3$ changed the way of N6-methyladenine binding to natural DNA bases

Nucleic Acids (Cont'd)

Dynamics of DNA polymerase I (Klenow fragment) under external force

Ping Xie[Key Laboratory of Soft Matter Physics]

J. Mol.Mod., **19,** 1379-1389, 2013.

During DNA synthesis, high-fidelity DNA polymerase (DNAP) translocates processively along the template by utilizing the chemical energy from nucleotide incorporation. Thus, understanding the chemomechanical coupling mechanism and the effect of external mechanical force on replication velocity are the most fundamental issues for high-fidelity DNAP. Here, based on our proposed model, we take Klenow fragment as an example to study theoretically the dynamics of high-fidelity DNAPs such as the replication velocity versus different types of external force

A Dynamic Structural Model of Expanded RNA CAG Repeats: A Refined X-ray Structure and Computational Investigations Using Molecular Dynamics and Umbrella Sampling Simulations

Ilyas Yildirim, HaJeung Park, Matthew D. Disney, and George C. Schatz

J. Am. Chem. Soc., 2013, 135 (9), pp 3528–3538

One class of functionally important RNA is repeating transcripts that cause disease through various mechanisms. For example, expanded CAG repeats can cause Huntington's and other disease through translation of toxic proteins. Herein, a crystal structure of r[5′UUGGGC(CAG)$_3$GUCC]$_2$, a model of CAG expanded transcripts, refined to 1.65 Å resolution is disclosed that shows both anti–anti and syn–anti orientations for 1 × 1 nucleotide AA internal loops. Molecular dynamics (MD) simulations using AMBER force field in explicit solvent were run for over 500 ns on the model systems r(5′GCGCAGCGC)$_2$ (MS1) and r(5′CCGCAGCGG)$_2$ (MS2). In these MD simulations, both anti–anti and syn–anti AA base pairs appear to be stable

Surfaces, Catalysts, and Materials Subjects

Nonequilibrium Molecular Simulations of New Ionic Lubricants at Metallic Surfaces: Prediction of the Friction

Ana C. F. Mendonça, Agílio A. H. Pádua, and Patrice Malfreyt [Université Blaise Pascal & CNRS]

J. Chem. Theor. and Comp, **9**, 1600–1610, 2013.

We report nonequilibrium molecular dynamics of ionic liquids interacting with metallic surfaces. A specific set of interaction parameters for ionic liquids composed of alkylammonium cations and alkylsulfonate anions with an iron surface, which has been previously developed (*J. Chem. Theory Comput.***2012**, *8*, 3348**)** is used here. We develop a procedure for a quantitative prediction of the friction coefficient at different loads and shear rates. The simulated friction coefficient agrees very well with the available experimental ones.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Interpretable, Probability-Based Confidence Metric for Continuous Quantitative Structure–Activity Relationship Models

Christopher E. Keefe [Department of Pharmacokinetic]r, Gregory W. Kauffman, and Rishi Raj Gupta

J.Chem. Infor. and Mod. **53**, 368–383, 2013.

A great deal of research has gone into the development of robust confidence in prediction and applicability domain (AD) measures for quantitative structure–activity relationship (QSAR) models in recent years. A concept that is frequently overlooked in the realm of the QSAR applicability domain is how the local activity landscape plays a role in how accurate a prediction is or is not. In this work, we describe an approach that pairs information about both the chemical similarity and activity landscape of a test compound's neighborhood into a single calculated confidence value.

QSAR model based on weighted MCS trees approach for the representation of molecule data sets

Bernardo Palacios-Bejarano, Gonzalo Cerruela García, Irene Luque Ruiz, Miguel Ángel Gómez-Nieto[University of Córdoba]

J. Comp. Aided Mol. Des.,**27**, 185-201, 2013.

In this paper we propose a new method for the generation of 2D-QSAR models for the prediction of activity values of chemicals. Maximum common substructures which are extracted from the data set are used for molecule classification in a tree, where the node of the tree represents molecules or common structures to groups of molecules and the arcs of the tree represent non isomorphic substructures between two nodes of the tree. All paths between pairwise leaf nodes are used to represent the equation system used as representational space in the building of the QSAR model.

Discovery of Novel Antimalarial Compounds Enabled by QSAR-Based Virtual Screening

Liying Zhang, Denis Fourches, Alexander Sedykh, Hao Zhu, Alexander Golbraikh, Sean Ekins, Julie Clark, Michele C. Connelly, Martina Sigal, Dena Hodges, Armand Guiguemde, R. Kiplin Guy,[St. Jude Children's Research Hospital,] and Alexander Tropsha

J.Chem. Infor. and Mod. **53**, 475–492, 2013.

Quantitative structure–activity relationship (QSAR) models have been developed for a data set of 3133 compounds defined as either active or inactive against *P. falciparum*. Because the data set was strongly biased toward inactive compounds, different sampling approaches were employed to balance the ratio of actives versus inactives, and models were rigorously validated using both internal and external validation approaches. The balanced accuracy for assessing the antimalarial activities of 70 external compounds was between 87% and 100% depending on the approach used to balance the data set.

Potentials and Parameters

Testing of the GROMOS Force-Field Parameter Set 54A8: Structural Properties of Electrolyte Solutions, Lipid Bilayers, and Proteins

Maria M. Reif, Moritz Winger, and Chris Oostenbrink [University of Natural Resources and Life Sciences,]

J. Chem. Theor. and Comp, **9**, 1247–1264, 2013.

The GROMOS 54A8 force field [Reif et al. *J. Chem. Theory Comput.***2012**, *8*, 3705–3723] is the first of its kind to contain nonbonded parameters for charged amino acid side chains that are derived in a rigorously thermodynamic fashion, namely a calibration against single-ion hydration free energies. The present study focuses on examining the ability of the GROMOS 54A8 force field to accurately model the structural properties of electrolyte solutions, lipid bilayers, and proteins.

SAFT-γ Force Field for the Simulation of Molecular Fluids: 2. Coarse-Grained Models of Greenhouse Gases, Refrigerants, and Long Alkanes

Carlos Avendaño, Thomas Lafitte, Claire S. Adjiman, Amparo Galindo, Erich A. Müller, and George Jackson[South Kensington Campus]

J. Phys. Chem. B., **117**, 2717–2733, 2013**.**

In the first paper of this series [C. Avendaño, T. Lafitte, A. Galindo, C. S. Adjiman, G. Jackson, and E. A. Müller, *J. Phys. Chem. B***2011**, *115*, 11154] we introduced the SAFT-γ force field for molecular simulation of fluids. In our approach, a molecular-based equation of state (EoS) is used to obtain coarse-grained (CG) intermolecular potentials that can then be employed in molecular simulation over a wide range of thermodynamic conditions of the fluid. The macroscopic experimental data for the vapor–liquid equilibria (saturated liquid density and vapor pressure) of a given system are represented with the SAFT-VR Mie EoS and used to estimate effective intermolecular parameters that provide a good description of the thermodynamic properties by exploring a wide parameter space for models based on the Mie (generalized Lennard-Jones) potential.

Three Entropic Classes of Side Chain in a Globular Protein

Dennis C. Glass, Marimuthu Krishnan, Jeremy C. Smith, and Jerome Baudry [University of Tennessee]

J. Phys. Chem. B., **117**, 3127–3134, 2013**.**

A!

The relationship between the NMR methyl group axial order parameter and the side chain conformational entropy is investigated in inhibitor-bound and apo human HIV protease using molecular dynamics simulation. Three distinct entropic classes of methyl-bearing side chains, determined by the topological distance of the methyl group from the protein backbone (i.e., the number of χ-bonds between the C_α and the carbon of the CH_3 group), are revealed by atomistic trajectory analyses performed in the local frame of reference of individual methyl probes.

Starting-structure dependence of nanosecond timescale intersubstate transitions and reproducibility of MD-derived order parameters

Tim Zeiske, Kate A. Stafford, Richard A. Friesner and Arthur G. Palmer III[Columbia University]

Proteins: Stru. Fun. & Bioinf., **81**, 499–509, 2013.

A!

Factors affecting the accuracy of molecular dynamics (MD) simulations are investigated by comparing generalized order parameters for backbone NH vectors of the B3 immunoglobulin-binding domain of streptococcal protein G (GB3) derived from simulations with values obtained from NMR spin relaxation (Yao L, Grishaev A, Cornilescu G, Bax A, J Am Chem Soc 2010;132:4295-4309.). Choices for many parameters of the simulations, such as buffer volume, water model, or salt concentration, have only minor influences on the resulting order parameters.

Molecular Dynamics

Natural bond orbital analysis in the ONETEP code: Applications to large protein systems

Louis P. Lee[1 ,[Cavendish Laboratory,]Daniel J. Cole[1], Mike C. Payne[1], Chris-Kriton Skylaris[2]

J. Comp. Chem., **34**,429–444, 2013.

First principles electronic structure calculations are typically performed in terms of molecular orbitals (or bands), providing a straightforward theoretical avenue for approximations of increasing sophistication, but do not usually provide any qualitative chemical information about the system. We can derive such information via post-processing using natural bond orbital (NBO) analysis, which produces a chemical picture of bonding in terms of localized Lewis-type bond and lone pair orbitals that we can use to understand molecular structure and interactions. We present NBO analysis of large-scale calculations with the ONETEP linear-scaling density functional theory package, which we have interfaced with the NBO 5 analysis program

Toward Fully in Silico Melting Point Prediction Using Molecular Simulations

Yong Zhang and Edward J. Maginn[University of Notre Dame]

J. Chem. Theor. and Comp, **9**, 1592–1599, 2013.

Melting point is one of the most fundamental and practically important properties of a compound. Molecular simulation methods have been developed for the accurate computation of melting points. However, all of these methods need an experimental crystal structure as input. In this work, we exploit the fact that free energy differences are often small between crystal structures. We show that accurate melting point predictions can be made by using a reasonable crystal structure from CSP as a starting point for a free energy-based melting point calculation.

Calculating Position-Dependent Diffusivity in Biased Molecular Dynamics Simulations

Jeffrey Comer, Christophe Chipot [Université de Lorraine], and Fernando D. González-Nilo

J. Chem. Theor. and Comp, **9**, 876–882, 2013.

Calculating transition rates and other kinetic quantities from molecular simulations requires knowledge not only of the free energy along the relevant coordinate but also the diffusivity as a function of that coordinate. A variety of methods are currently used to map the free-energy landscape in molecular simulations. Here, we describe a method to calculate position-dependent diffusivities in simulations including known time-dependent biasing forces, which relies on a previously proposed Bayesian inference scheme.

A!

Molecular Dynamics (Cont'd)

Coulomb replica-exchange method: Handling electrostatic attractive and repulsive forces for biomolecules

Satoru G. Itoh,[nstitute for Molecular Science,] Hisashi Okumura

J. Comp. Chem., **34**,622–639, 2013.

We propose a new type of the Hamiltonian replica-exchange method (REM) for molecular dynamics (MD) and Monte Carlo simulations, which we refer to as the Coulomb REM (CREM). In this method, electrostatic charge parameters in the Coulomb interactions are exchanged among replicas while temperatures are exchanged in the usual REM. By varying the atom charges, the CREM overcomes free-energy barriers and realizes more efficient sampling in the conformational space than the REM.

A Candidate Ion-Retaining State in the Inward-Facing Conformation of Sodium/Galactose Symporter: Clues from Atomistic Simulations

Ina Bisha, Alessandro Laio, Alessandra Magistrato [CNR-IOM-Democritos National Simulation Center c/o SISSA], Alejandro Giorgetti, and Jacopo Sgrignani

J. Chem. Theor. and Comp, **9**, 1240–1246, 2013.

The recent *Vibrio parahaemolyticus* sodium/galactose (vSGLT) symporter crystal structure captures the protein in an inward-facing substrate-bound conformation, with the sodium ion placed, by structural alignment, in a site equivalent to the Na2 site of the leucine transporter (LeuT). A recent study, based on molecular dynamics simulations, showed that the sodium ion spontaneously leaves its initial position diffusing outside vSGLT, toward the intracellular space. Here, using metadynamics, we identified a more stable Na^+ binding site corresponding to a putative ion-retaining state of the transporter.

Exploring the Diffusion of Molecular Oxygen in the Red Fluorescent Protein mCherry Using Explicit Oxygen Molecular Dynamics Simulations

Chola K. Regmi, Yuba R. Bhandari, Bernard S. Gerstman, and Prem P. Chapagain[Florida International University]

J. Phys. Chem. B., **117**, 2247–2253, 2013**.**

The development of fluorescent proteins (FPs) has revolutionized cell biology research. The monomeric variants of red fluorescent proteins (RFPs), known as mFruits, have been especially valuable for tagging and tracking cellular processes in vivo. Determining oxygen diffusion pathways in FPs can be important for improving photostability and for understanding maturation of the chromophore. We use molecular dynamics (MD) calculations to investigate the diffusion of molecular oxygen in one of the most useful monomeric RFPs, mCherry.

Free Energy Perturbation

Modeling Local Structural Rearrangements Using FEP/REST: Application to Relative Binding Affinity Predictions of CDK2 Inhibitors

Lingle Wang, Yuqing Deng, Jennifer L. Knight, Yujie Wu, Byungchan Kim, Woody Sherman, John C. Shelley, Teng Lin, and Robert Abel

J. Chem. Theor. and Comp, **9**, 1282–1293, 2013.

Accurate and reliable calculation of protein–ligand binding affinities remains a hotbed of computer-aided drug design research. Despite the potentially large impact FEP (free energy perturbation) may have in drug design projects, practical applications of FEP in industrial contexts have been limited. In this work, we use a recently developed method, FEP/REST (free energy perturbation/replica exchange with solute tempering), to calculate the relative binding affinities for a set of congeneric ligands binding to the CDK2 receptor.

Free Energy Perturbation (Cont'd)

Free Enthalpy Differences between α-, π-, and 3_{10}-Helices of an Atomic Level Fine-Grained Alanine Deca-Peptide Solvated in Supramolecular Coarse-Grained Water

Zhixiong Lin, Sereina Riniker, and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

J. Chem. Theor. and Comp, **9**, 1328–1333, 2013.

Atomistic molecular dynamics simulations of peptides or proteins in aqueous solution are still limited to the multi-nanosecond time scale and multi-nanometer range by computational cost. Combining atomic solutes with a supramolecular solvent model in hybrid fine-grained/coarse-grained (FG/CG) simulations allows atomic detail in the region of interest while being computationally more efficient. We used enveloping distribution sampling (EDS) to calculate the free enthalpy differences between different helical conformations, i.e., α-, π-, and 3_{10}-helices, of an atomic level FG alanine deca-peptide solvated in a supramolecular CG water solvent.

Martini Force Field Parameters for Glycolipids

César A. López, Zofie Sovova, Floris J. van Eerden, Alex H. de Vries, and Siewert J. Marrink [University of Groninge]

J. Chem. Theor. and Comp, **9**, 1694–1708, 2013.

We present an extension of the Martini coarse-grained force field to glycolipids. The glycolipids considered here are the glycoglycerolipids monogalactosyldiacylglycerol , sulfoquinovosyldiacylglycerol , digalactosyldiacylglycerol, and phosphatidylinositol and its phosphorylated forms , as well as the glycosphingolipids galactosylceramide and monosialotetrahexosylganglioside. The parametrization follows the same philosophy as was used previously for lipids, proteins, and carbohydrates focusing on the reproduction of partitioning free energies of small compounds between polar and nonpolar solvents.

Role of tyrosine hot-spot residues at the interface of colicin E9 and immunity protein 9: A comparative free energy simulation study

Manuel P. Luitz and Martin Zacharias[Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **81**, 461–468, 2013.

The endonuclease activity of the bacterial colicin 9 enzyme is controlled by the specific and high-affinity binding of immunity protein 9 (Im9). Molecular dynamics simulation studies in explicit solvent were used to investigate the free energy change associated with the mutation of two hot-spot interface residues [tyrosine (Tyr): Tyr54 and Tyr55] of Im9 to Ala. In addition, the effect of several other mutations (Leu33Ala, Leu52Ala, Val34Ala, Val37Ala, Ser48Ala, and Ile53Ala) with smaller influence on binding affinity was also studied.

QM and QM/MM

STAAR: Statistical analysis of aromatic rings

David D. Jenkins, Jason B. Harris,Elizabeth E. Howell, Robert J. Hinde,Jerome Baudry [Oak Ridge National Laboratory]

J. Comp. Chem., **34**,518–522, 2013.

The statistical analysis of aromatic rings program allows for an automated search for anion-π interactions between phenylalanine residues and carboxylic acid moieties of neighboring aspartic acid or glutamic acid residues in protein data bank (PDB) structures. The program outputs lists of Phe/Glu or Phe/Asp pairs involved in potential anion-π interactions, together with geometrical (distance and angle between the Phe's center of mass and Glu or Asp's center of charge) and energetic (quantum mechanical Kitaura-Morokuma interaction energy between the residues) descriptions of each anion-π interaction.

Tuned and Balanced Redistributed Charge Scheme for Combined Quantum Mechanical and Molecular Mechanical (QM/MM) Methods and Fragment Methods: Tuning Based on the CM5 Charge Model

Bo Wang and Donald G. Truhlar [University of Minnesota]

J. Chem. Theor. and Comp, **9**, 1036–943, 2013.

Tuned and balanced redistributed charge schemes have been developed for modeling the electrostatic fields of bonds that are cut by a quantum mechanical–molecular mechanical boundary in combined quantum mechanical and molecular mechanical (QM/MM) methods. First, the charge is balanced by adjusting the charge on the MM boundary atom to conserve the total charge of the entire QM/MM system. The new aspect of the present study is a new way to carry out the tuning process; in particular, the CM5 charge model, rather than the Mulliken population analysis applied in previous studies, is used for tuning the capping atom that terminates the dangling bond of the QM region.

Hybrid QM/QM Simulations of Excited-State Intramolecular Proton Transfer in the Molecular Crystal 7-(2-Pyridyl)-indole

Michał A. Kochman and Carole A. Morrison[The University of Edinburgh]

J. Chem. Theor. and Comp, **9**, 1182–1192, 2013.

A subtractive implementation of the QM/QM hybrid method for the description of photochemical reactions occurring in molecular crystals is presented and tested by applying it in a simulation study of the ultrafast intramolecular excited-state proton transfer reaction in the crystal form of 7-(2-pyridyl)-indole, an organic compound featuring an intramolecular hydrogen bond within a six-membered ring. By propagating molecular dynamics on the excited-state potential energy surface, a mean proton transfer time was calculated as 80 fs.

Photoabsorption of Acridine Yellow and Proflavin Bound to Human Serum Albumin Studied by Means of Quantum Mechanics/Molecular Dynamics

Kęstutis Aidas [Vilnius University], Jógvan Magnus H. Olsen, Jacob Kongsted, and Hans Ågren

J. Phys. Chem. B., **117**, 2069–2080, 2013**.**

Attempting to unravel mechanisms in optical probing of proteins, we have performed pilot calculations of two cationic chromophores—acridine yellow and proflavin—located at different binding sites within human serum albumin, including the two primary drug binding sites as well as a heme binding site. The computational scheme adopted involves classical molecular dynamics simulations of the ligands bound to the protein and subsequent linear response polarizable embedding density functional theory calculations of the excitation energies

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Comparative or Homology Modeling

Benchmarking of HPCC: A novel 3D molecular representation combining shape and pharmacophoric descriptors for efficient molecular similarity assessments

Arnaud S. Karaboga [CNRS-Nancy University], Florent Petronin ,Gino Marchetti ,Michel Souchet ,Bernard Maigret

J. Mol.Graph. and Mod., **41,** 20-30, 2013.

Since 3D molecular shape is an important determinant of biological activity, designing accurate 3D molecular representations is still of high interest. Several chemoinformatic approaches have been developed to try to describe accurate molecular shapes. Here, we present a novel 3D molecular description, namely harmonic pharma chemistry coefficient (HPCC), combining a ligand-centric pharmacophoric description projected onto a spherical harmonic based shape of a ligand. The performance of HPCC was evaluated by comparison to the standard ROCS software in a ligand-based virtual screening (VS) approach using the publicly available directory of useful decoys (DUD) data set comprising over 100,000 compounds distributed across 40 protein targets.

Energetics of the Presequence-Binding Poses in Mitochondrial Protein Import Through Tom20

Yasuaki Komuro, Naoyuki Miyashita, Takaharu Mori, Eiro Muneyuki, Takashi Saitoh, Daisuke Kohda, and Yuji Sugita [RIKEN Advanced Science Institute]

J. Phys. Chem. B., **117**, 2864–2871, 2013**.**

A!

Tom20 is located at the outer membrane of mitochondria and functions as a receptor for the N-terminal presequence of mitochondrial-precursor proteins. Recently, three atomic structures of the Tom20-presequence complex were determined using X-ray crystallography and classified into A-, M-, and Y-poses in terms of their presequence-binding modes. Combined with biochemical and NMR data, a dynamic-equilibrium model between the three poses has been proposed. To investigate this mechanism in further detail, we performed all-atom molecular dynamics (MD) simulations and replica-exchange MD (REMD) simulations of the Tom20-presequence complex in explicit water

Ligand Docking

Three- and four-body corrected fragment molecular orbital calculations with a novel subdividing fragmentation method applicable to structure-based drug design

Chiduru Watanabe [The University of Tokyo], Kaori Fukuzawa, Yoshio Okiyama, Takayuki Tsukamoto, Akifumi Kato, Shigenori Tanaka, Yuji Mochizuki, Tatsuya Nakano

J. Mol.Graph. and Mod., **41,** 31-42, 2013.

A!

We develop an inter-fragment interaction energy (IFIE) analysis based on the three- and four-body corrected fragment molecular orbital (FMO3 and FMO4) method to evaluate the interactions of functional group units in structure-based drug design context. The novel subdividing fragmentation method for a ligand (in units of their functional groups) and amino acid residues (in units of their main and side chains) enables us to understand the ligand-binding mechanism in more detail without sacrificing chemical accuracy of the total energy and IFIEs by using the FMO4 method. We perform FMO4 calculations with the second order Møller-Plesset perturbation theory for an estrogen receptor (ER) and the 17β-estradiol (EST) complex using the proposed fragmentation method and assess the interaction for each ligand-binding site by the FMO4-IFIE analysis.

Ligand Docking (Cont'd)

Conformational flexibility of the ErbB2 ectodomain and trastuzumab antibody complex as revealed by molecular dynamics and principal component analysis

Juan Felipe Franco-Gonzalez, Victor L. Cruz, Javier Ramos[Instituto de Estructura de la Materia,]

J. Mol.Mod., **19,** 1227-1236, 2013.

Human epidermal growth factor receptor 2 (ErbB2) is a transmembrane oncoprotein that is over expressed in breast cancer. A successful therapeutic treatment is a monoclonal antibody called trastuzumab which interacts with the ErbB2 extracellular domain (ErbB2-ECD). A better understanding of the detailed structure of the receptor-antibody interaction is indeed of prime interest for the design of more effective anticancer therapies. In order to discuss the flexibility of the complex ErbB2-ECD/trastuzumab, we present, in this study, a multi-nanosecond molecular dynamics simulation (MD) together with an analysis of fluctuations, through a principal component analysis (PCA) of this system.

Taste for Chiral Guests: Investigating the Stereoselective Binding of Peptides to β-Cyclodextrins

Muhannad Altarsha, Violeta Yeguas, Francesca Ingrosso, Ramón López, and Manuel F. Ruiz-López [Université de Lorraine]

J. Phys. Chem. B., **117**, 3091–3097, 2013**.**

Obtaining compounds of diastereomeric purity is extremely important in the field of biological and pharmaceutical industry, where amino acids and peptides are widely employed. In this work, we theoretically investigate the possibility of chiral separation of peptides by β-cyclodextrins (β-CDs), providing a description of the associated interaction mechanisms by means of molecular dynamics (MD) simulations. The formation of host/guest complexes by including a model peptide in the macrocycle cavity is analyzed and discussed. We consider the terminally blocked phenylalanine dipeptide (Ace-Phe-Nme), in the l- and d-configurations, to be involved in the host/guest recognition process.

Free Energy Calculations Reveal the Origin of Binding Preference for Aminoadamantane Blockers of Influenza A/M2TM Pore

Paraskevi Gkeka, Stelios Eleftheratos, Antonios Kolocouris, and Zoe Cournia [University of Athens]

J. Chem. Theor. and Comp, **9**, 1272–1281, 2013.

Aminoadamantane derivatives, such as amantadine and rimantadine, have been reported to block the M2 membrane protein of influenza A virus (A/M2TM), but their use has been discontinued due to reported resistance in humans. Understanding the mechanism of action of amantadine derivatives could assist the development of novel potent inhibitors that overcome A/M2TM resistance. Here, we use Free Energy Perturbation calculations coupled with Molecular Dynamics simulations (FEP/MD) to rationalize the thermodynamic origin of binding preference of several aminoadamantane derivatives inside the A/M2TM pore.

Constant pH molecular dynamics (CpHMD) and molecular docking studies of CquiOBP1 pH-induced ligand releasing mechanism

Wen-Ting Chu, Ji-Long Zhang, Qing-Chuan Zheng, [Jilin University]

J. Mol.Mod., **19,** 1301-1309,2013.

The odorant binding protein of *Culex quinquefasciatus* (CquiOBP1), expressed on the insect antenna, is crucial for the investigation of trapping baited with oviposition semi-chemicals and controlling mosquito populations. The acidic titratable residues pKa prediction and the ligand binding poses investigation in two systems (pH 7 and pH 5) are studied by constant pH molecular dynamics (CpHMD) and molecular docking methods. Research results reveal that the change of the protonation states would disrupt some important H-bonds, such as Asp 66-Asp 70, Glu 105-Asn 102, etc.

Ligand Docking (Cont'd)

A solvated ligand rotamer approach and its application in computational protein design

Xiaoqiang Huang, Ji Yang, Yushan Zhu [Tsinghua University]

J. Mol.Mod., **19,** 1355-1367, 2013.

The structure-based design of protein–ligand interfaces with respect to different small molecules is of great significance in the discovery of functional proteins. By statistical analysis of a set of protein–ligand complex structures, it was determined that water-mediated hydrogen bonding at the protein–ligand interface plays a crucial role in governing the binding between the protein and the ligand. Based on the novel statistic results, a solvated ligand rotamer approach was developed to explicitly describe the key water molecules at the protein–ligand interface and a water-mediated hydrogen bonding model was applied in the computational protein design context to complement the continuum solvent model.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 40, March, 2013.

1–9 **Elucidating the catalytic mechanism of β-secretase (BACE1): A quantum mechanics/molecular mechanics (QM/MM) approach.,** Arghya Barman, Rajeev Prabhakar [University of Miami]

See Applications / Enzyme Catalyse.

10–21 **The role of loop closure propensity in the refolding of Rop protein probed by molecular dynamics simulations,** Rashmi Tambe Shukla, Chetana Baliga, Yellamraju U. Sasidhar[Indian Institute of Technology Bombay]

See Applications / Protein Folding.

22–29 **Investigation of the influence of molecular topology on ligand binding ,** Rurika Oka[a, b], Ola Engkvist[b], Hongming Chen[b][Lund University,]

See Applications / Ligand binding.

30–39 **Toward an understanding of the sequence and structural basis of allosteric proteins,** Xiaobai Li ,Yingyi Chen ,Shaoyong Lu ,Zhimin Huang ,Xinyi Liu ,Qi Wang ,Ting Shi , Jian Zhang[Shanghai JiaoTong University]

See Applications / Protein Dynamics.

40–47 ***In silico* identification of novel inhibitors against *Plasmodium falciparum* dihydroorate dehydrogenase** Abdul Wadood[University of Karachi] Zaheer- ulhaq

See Applications / Medicinal Chemmistry and Drug Design.

48–53 **ViewMotions Rainbow: A new method to illustrate molecular motions in proteins,** Gregory M. Cockrell, Evan R. Kantrowitz[Merkert Chemistry Center, Chestnut Hill]

See Applications / Protein Dynamics.

54–63 **Structure–property relationships of energetic nitrogen-rich salts composed of triaminoguanidinium or ammonium cation and tetrazole-based anions ,** Yuling Shao, Weihua Zhu ,Heming Xiao[Nanjing University of Science and Technology]

Density functional theory and volume-based thermodynamics calculations have been performed to study the crystal densities, heats of formation (HOFs), energetic properties, and thermodynamics of formation for a series of ionic salts composed of triaminoguanidinium or ammonium cations and tetrazole-based anions.

64–71 **Toward rational design of organic dye sensitized solar cells (DSSCs): An application to the TA-St-CA dye ,** Narges Mohammadi, Peter J. Mahon, Feng Wang[Swinburne University of Technology]

A computer aided rational design has been performed on TA-St-CA dye sensitizer in order to improve the desirable properties for new organic dye sensitized solar cell (DSSC). A number of electron-donating (ED) and electron-withdrawing (EW) units based on Dewar's rules are substituted into the π-conjugated oligo-phenylenevinylene bridge of the reference TA-St-CA dye.

72–79 **Identification of potential bivalent inhibitors from natural compounds for acetylcholinesterase through *in silico* screening using multiple pharmacophores,** V. Lakshmi, V. Santhosh Kannan, R. Boopathy[Bharathiar University]

See Applications / Medicinal Chemmistry and Drug Design.

80–90 **AutoMap: A tool for analyzing protein–ligand recognition using multiple ligand binding modes ,** Mark Agostino ,Ricardo L. Mancera ,Paul A. Ramsland ,Elizabeth Yuriev[Monash University]

See Applications / Protein Ligand.

91–98 **Assessment of new anti-HER2 ligands using combined docking, QM/MM scoring and MD simulation,** Marawan Ahmed, Maiada M. Sadek, Rabah A. Serrya, Abdel-Hamid N. Kafafy, Khaled A. Abouzid, Feng Wang[Swinburne University of Technology]

See Applications / Ligand binding.

99–109 **Mechanism of the irreversible inhibition of human cyclooxygenase-1 by aspirin as predicted by QM/MM calculations ,** L. Tóth ,L. Muszbek ,I. Komáromi[University of Debrecen]

See Applications / Enzyme Catalyse.

110–115 **Theoretical studies on the photoisomerization-switchable second-order nonlinear optical responses of DTE-linked polyoxometalate derivatives ,** Teng-Ying Ma, Na-Na Ma, Li-Kai Yan Wei Guan, Zhong-Min Su[Northeast Normal University]

The switchable second-order nonlinear optical (NLO) responses of the photoisomerized chromophore dithienylperfluorocyclopentene (DTE) derivatives, organic–inorganic systems of Lindqvist-type $[Mo_6O_{19}]^{2-}$, have been investigated by tuning open-ring and the closed-ring form. In the present paper, we performed

density functional theory (DFT) combined with finite field (FF) methods to calculate the second-order NLO coefficients for these organic-inorganic compounds.

116–124 **Chemosensitizing acridones: In vitro calmodulin dependent *c*AMP phosphodiesterase inhibition, docking, pharmacophore modeling and 3D QSAR studies ,** V.V.S. Rajendra Prasad, G. Deepa Reddy, D. Appaji, G.J. Peters ,Y.C. Mayur [Dr. Bhanuben Nanavati College of Pharmacy]

See Applications / Medicinal Chemmistry and Drug Design.

125–130 **The prediction of palmitoylation site locations using a multiple feature extraction method,** Shao-Ping Shi Xing-Yu Sun, Jian-Ding QiuSheng-Bao Suo, Xiang Chen, Shu-Yun Huang, Ru-Ping Liang[Nanchang University]

See Applications / Bioinformatics.

131–139 **Computer modeling on the tautomerization of sulbactam intermediate in SHV-1 β-lactamases: E166A mutant vs. wild type,** Rui Li, Yeng-Tseng Wang, Cheng-Lung Chen[Liaocheng University]

See Applications / Protein Dynamics.

Journal of Molecular Graphics and Modelling, 41, April, 2013.

1–11 **Algorithms of GPU-enabled reactive force field (ReaxFF) molecular dynamics,** Mo Zheng[Graduate University of Chinese Academy of Sciences] ,Xiaoxia Li, Li Guo

See Applications / Bioinformatics.

12–19 **Towards the identification of the binding site of benzimidazoles to β-tubulin of *Trichinella spiralis*: Insights from computational and experimental data** Rodrigo Aguayo-Ortiz ,Oscar Méndez-Lucio ,José L. Medina-Franco ,Rafael Castillo ,Lilián Yépez-Mulia ,Francisco Hernández-Luis ,Alicia Hernández-Campos[a,] [Universidad Nacional Autónoma de México]

See Applications / Ligand binding.

20–30 **Benchmarking of HPCC: A novel 3D molecular representation combining shape and pharmacophoric descriptors for efficient molecular similarity assessments ,** Arnaud S. Karaboga [CNRS-Nancy University], Florent Petronin ,Gino Marchetti ,Michel Souchet ,Bernard Maigret

See Applications / Homology Modeling.

31-42 **Three- and four-body corrected fragment molecular orbital calculations with a novel subdividing fragmentation method applicable to structure-based drug design,** Chiduru Watanabe [The University of Tokyo], Kaori Fukuzawa, Yoshio Okiyama, Takayuki Tsukamoto, Akifumi Kato, Shigenori Tanaka, Yuji Mochizuki, Tatsuya Nakano

See Methodology / Ligand binding.

43-54 **Synthesis and evaluation of resveratrol derivatives as new chemical entities for cancer** , Chaitanya Mulakayala, B. Babajan, P. Madhusudana, C.M. Anuradha, Raja Mohan Rao, Ravi Prakash Nune, Sunil Kumar Manna, Naveen Mulakayala, Chitta Suresh Kumar[Sri Krishandevaraya University]

See Applications / Medicinal Chemmistry and Drug Design.

55-60 **Structural basis of femtomolar inhibitors for acetylcholinesterase subtype selectivity: Insights from computational simulations,** Xiao-Lei Zhu, Ning-Xi Yu, Ge-Fei Hao, Wen-Chao Yang, Guang-Fu Yang[Central China Normal University]

See Applications / Medicinal Chemmistry and Drug Design.

61-67 **3D-QSAR studies of azaoxoisoaporphine, oxoaporphine, and oxoisoaporphine derivatives as anti-AChE and anti-AD agents by the CoMFA method ,** Yan-Ping Li, Xiang Weng, Fang-Xian Ning, Jie-Bin Ou, Jin-Qiang Hou, Hai-Bin Luo[Sun Yat-sen University], Ding Li, Zhi-Shu Huang, Shi-Liang Huang, Lian-Quan Gu

See Applications / Medicinal Chemmistry and Drug Design.

68-71 **As good as it gets? Folding molecular dynamics simulations of the LytA choline-binding peptide result to an exceptionally accurate model of the peptide structure,** Ilias Patmanidis, Nicholas M. Glykos[Democritus University of Thrace]

See Applications / Protein Folding.

72-78 **Molecular dynamic simulation of mGluR5 amino terminal domain: essential dynamics analysis captures the agonist or antagonist behaviour of ligands ,** Alessandro Casoni, Francesca Clerici, Alessandro Contini[Università degli Studi di Milano]

See Methodology / Ligand binding.

79-88 **Third-order nonlinear optical properties of molecules containing aromatic diimides: Effects of the aromatic core size and a redox-switchable modification ,** Yong-Qing Qiu, Zhuo Li, Na-Na Ma, Shi-Ling Sun, Meng-Ying Zhang, Peng-Jun Liu[Hainan Normal University]

The third-order nonlinear optical (NLO) properties of aromatic diimide molecules have been studied for the first time using density functional theory (DFT) with a finite field (FF).

89-96 **DFT modeling of CO_2 adsorption on Cu, Zn, Ni, Pd/DOH zeolite ,** Daniel Smykowski [Wrocław University of Technology], Bartłomiej Szyja, Jerzy Szczygieł

This study is the analysis of the adsorption process of the CO_2 molecule on the cationic sites of the DOH zeolite. Based on the DFT method, we have been able to identify several adsorption sites containing extra-framework cations and evaluate the value of the adsorption energy with respect to the distance from the adsorption site.

Journal of Computational Chemistry, 34(6), March, 2013.

429–444 **Natural bond orbital analysis in the ONETEP code: Applications to large protein systems,** Louis P. Lee [Cavendish Laboratory], Daniel J. Col , Mike C. Payne, Chris-Kriton Skylaris

See Methodology / Molecular Dynamics.

445–450 **GRID: A high-resolution protein structure refinement algorithm ,** Mohsen Chitsaz,Stephen L. Mayo [California Institute of Technology]

The energy-based refinement of protein structures generated by fold prediction algorithms to atomic-level accuracy remains a major challenge in structural biology. Energy-based refinement is mainly dependent on two components: (1) sufficiently accurate force fields, and (2) efficient conformational space search algorithms. Focusing on the latter, we developed a high-resolution refinement algorithm called GRID.

451–459 **Consistent gaussian basis sets of Triple-Zeta valence with polarization quality for solid-State Calculations** Michael F. Peintinger,Daniel Vilela Oliveira,Thomas Bredow [University of Bonn, Beringstr]

Consistent basis sets of triple-zeta valence with polarization quality for main group elements and transition metals from row one to three have been derived for periodic quantum-chemical solid-state calculations with the crystalline-orbital program CRYSTAL. They are based on the def2-TZVP basis sets developed for molecules by the Ahlrichs group.

460–465 **An economic prediction of refinement coefficients in wavelet-based adaptive methods for electron structure calculations ,** János Pipek ,Szilvia Nagy[Budapest University of Technology and Economics]

The wave function of a many electron system contains inhomogeneously distributed spatial details, which allows to reduce the number of fine detail wavelets in multiresolution analysis approximations. We describe

an effective prediction algorithm for the next resolution level wavelet coefficients, based on the approximate wave function expanded up to a given level.

466–470 **Revealing noncovalent interactions in quantum crystallography: Taurine revisite ,** Jack Yang, Mark P. Waller [Westfälische Wilhelms-Universität Münster]

The charge density distribution in taurine (2-aminoethane-sulfonic acid) is further studied with the molecular orbital occupation number refinement scheme.

471–491 **Structure and spectroscopic aspects of water-halide ion clusters: A study based on a conjunction of stochastic and quantum chemical methods,** Soumya Ganguly Neogi, Pinaki Chaudhury[University of Calcutta]

In this article, we propose a stochastic search based method, namely genetic algorithm in conjunction with density functional theory to evaluate structures of water-halide microclusters, with the halide ion being Cl^-, Br^-, and I^-.

492–504 **Block-adaptive quantum mechanics: An adaptive divide-and-conquer approach to interactive quantum chemistry ,** Maël Bosson [CNRS Laboratoire Jean Kuntzmann] Sergei Grudinin, Stephane Redon

We present a novel Block-Adaptive Quantum Mechanics (BAQM) approach to interactive quantum chemistry. Although quantum chemistry models are known to be computationally demanding, we achieve interactive rates by focusing computational resources on the most active parts of the system.

505–517 **A detailed investigation on the global minimum structures of mixed rare-gas clusters: Geometry, energetics, and site occupancy ,** Jorge M. C. Marques [Universidade de Coimbra] Francisco B. Pereira

We performed a global minimum search of mixed rare-gas clusters by applying an evolutionary algorithm (EA), which was recently proposed for binary atomic systems (Marques and Pereira, *Chem. Phys. Lett.* 2010, 485, 211). Before being applied to the potentials used in this work, the EA was further tested against results previously reported for the Ar_NXe_{38-N} clusters and several new putative global minima were discovered.

518–522 **STAAR: Statistical analysis of aromatic rings,** David D. Jenkins, Jason B. Harris,Elizabeth E. Howell, Robert J. Hinde,Jerome Baudry [Oak Ridge National Laboratory]

See Methodology / QM and QM/MM.

Journal of Computational Chemistry, 34(7), March, 2013.

523–532 **Solvent-driven symmetry of self-assembled nanocrystal superlattices—A computational study ,**Ananth P. Kaushik, Paulette Clancy [Cornell University]

The preference of experimentally realistic sized 4-nm facetted nanocrystals (NCs), emulating Pb chalcogenide quantum dots, to spontaneously choose a crystal habit for NC superlattices (Face Centered Cubic (FCC) vs. Body Centered Cubic (BCC)) is investigated using molecular simulation approaches.

533–544 **Insights into the dynamics of evaporation and proton migration in protonated water clusters from large-scale born–oppenheimer direct dynamics,** Vladimir V. Rybkin [University of Oslo], Anton O. Simakov, Vebjørn Bakken, Simen Reine, Thomas Kjærgaard, Trygve Helgaker, Einar Uggerud

Large-scale on-the-fly Born–Oppenheimer molecular dynamics simulations using recent advances in linear scaling electronic structure theory and trajectory integration techniques have been performed for protonated water clusters around the magic number $(H_2O)_nH^+$, for n = 20 and 21.

545–557 **Rate coefficients of the CF_3CHFCF_3 + H → CF_3CFCF_3 + H_2 reaction at different temperatures calculated by transition state theory with *ab initio* and DFT reaction paths,** Maggie Ng ,Daniel K. W. Mok [Hong Kong Polytechnic University],Edmond P. F. Lee ,John M. Dyke[2]

The minimum energy path (MEP) of the reaction, CF_3CHFCF_3 + H → transition state (TS) → CF_3CFCF_3 + H_2, has been computed at different *ab initio* levels and with density functional theory (DFT) using different functionals.

558–56 **Conventional strain energies of azetidine and phosphetane: Can density functional theory yield reliable results?,** Shelley A. Smith, Karen E. Hand,Melissa L. Love,Glake Hill,David H. Magers[Jackson State University]

The conventional strain energies for azetidine and phosphetane are determined within the isodesmic, homodesmotic, and hyperhomodesmotic models. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies and zero-point vibrational energies are computed for all pertinent molecular systems using self-consistent field theory, second-order perturbation theory, and density functional theory and using the correlation consistent basis sets cc-pVDZ, cc-pVTZ, and cc-pVQZ.

566–575 **An accurate and efficient method to predict the electronic excitation energies of BODIPY fluorescent dyes,** Jia-Nan Wang, Jun-Ling Jin, Yun Geng, Shi-Ling Sun, Hong-Liang Xu[Northeast Normal University,]Ying-Hua Lu, Zhong-Min Su

Recently, the extreme learning machine neural network (ELMNN) as a valid computing method has been proposed to predict the nonlinear optical property successfully (Wang et al., *J. Comput. Chem.* **2012**, 33, 231). In this work, first, we follow this line of work to predict the electronic excitation energies using the ELMNN method.

576–582 **Calculating standard reduction potentials of [4Fe–4S] proteins,** Bradley Scott Perrin Jr., Shuqiang Niu, Toshiko Ichiye [Department of Chemistry, Georgetown University]

The oxidation–reduction potentials of electron transfer proteins determine the driving forces for their electron transfer reactions. Here, a method for calculating the reduction potential *versus* the standard hydrogen electrode, *E*°, of a metalloprotein using a combination of density functional theory and continuum electrostatics is presented.

583–592 **Water PMF for predicting the properties of water molecules in protein binding site,** Mingyue Zheng[1,†], Yanlian Li[2,†], Bing Xiong[2,*], Hualiang Jiang[1], Jingkang Shen[2,*] [Shanghai Institute of Materia Medica,]

See Applications / Protein Dynamics.

593–603 **$(Ala)_4$-X-$(Ala)_4$ as a model system for the optimization of the χ_1 and χ_2 amino acid side-chain dihedral empirical force field parameters,** jihyun Shim[1], Xiao Zhu[1], Robert B. Best[2], Alexander D. MacKerell Jr.[1] [University of Maryland]

See Applications / Protein Dynamics.

604–610 **PaDEL-DDPredictor: Open-source software for PD-PK-T prediction ,** Yuye He, Chin Yee Liew, Nitin Sharma, Sze Kwang Woo, Yi Ting Chau, Chun Wei Yap [National University of Singapore]

ADMET (absorption, distribution, metabolism, excretion, and toxicity)-related failure of drug candidates is a major issue for the pharmaceutical industry today. Prediction of PD-PK-T properties using *in silico* tools has become very important in pharmaceutical research to reduce cost and enhance efficiency. PaDEL-DDPredictor is an *in silico* tool for rapid prediction of PD-PK-T properties of compounds from their chemical structures.

Journal of Computational Chemistry, 34(8), March, 2013.

523–532 **Solvent-driven symmetry of self-assembled nanocrystal superlattices—A computational study,** Ananth P. Kaushik, Paulette Clancy [Cornell University]

The preference of experimentally realistic sized 4-nm facetted nanocrystals (NCs), emulating Pb chalcogenide quantum dots, to spontaneously choose a crystal habit for NC superlattices (Face Centered Cubic (FCC) vs. Body Centered Cubic (BCC)) is investigated using molecular simulation approaches.

696–705 **Complexes of 4-substituted phenolates with HF and HCN: Energy decomposition and electronic structure analyses of hydrogen bonding—** , Halina Szatyłowicz [Warsaw University of Technology,]Tadeusz M. Krygowski, Célia Fonseca Guerra, F. Matthias Bickelhaupt

We have computationally studied *para*-X-substituted phenols and phenolates (X = NO, NO_2, CHO, COMe, COOH, $CONH_2$, Cl, F, H, Me, OMe, and OH) and their hydrogen-bonded complexes with B^- and HB (B = F and CN), respectively, at B3LYP/6-311++G** and BLYP-D/QZ4P levels of theory.

Journal of Molecular Modelling, 19(3), March 2013.

973-983 **Interaction of dihydrofolate reductase and aminoglycoside adenyltransferase enzyme from *Klebsiella pneumoniae* multidrug resistant strain DF12SA with clindamycin: a molecular modelling and docking study ,** Shailesh K. Shahi, Vinay K. Singh, Ashok Kumar [Banaras Hindu University Varanasi]

See Applications / Medicinal Chemmistry and Drug Design.

985-990 **Polymerization of miniature fullerenes in the cavity of nanotubes,** O. E. Glukhova, A. S. Kolesnikova, M. M. Slepchenkov [Department of Physics]

See Applications / Carbon Nanoparticles.

991-997 **Drug permeability prediction using PMF method ,** Fancui Meng, Weiren Xu [Tianjin Key Laboratory of Molecular Design and Drug Discovery]

See Applications / Medicinal Chemmistry and Drug Design.

999-1007 **In silico characterization of a novel β-1,3-glucanase gene from *Bacillus amyloliquefaciens*—a bacterial endophyte of *Hevea brasiliensis* antagonistic to *Phytophthora meadii,*** Amith Abraham, Sunilkumar Puthenpurackal Narayanan[Mahatma Gandhi University]

See Applications / Homology Modeling.

1009-1018 **Direct ab initio study on the rate constants of radical $C_2(A^3\Pi_u) + C_3H_8$ reaction ,** Rui-Ping Huo, Xiang Zhang, Xu-Ri Huang, Ji-Lai Li [Jilin University]

The mechanism and kinetics of the radical $^3C_2 + C_3H_8$ reaction have been investigated theoretically by direct ab initio kinetics over a wide temperature range. The potential energy surfaces have been constructed at the CCSD(T)/B3//UMP2/B1 levels of theory. The electron transfer was also analyzed by quasi–restricted orbital (QRO) in detail.

Chemical functionalization of the boron nitride nanotube (BNNT) allows a wider flexibility in engineering its electronic and magnetic properties as well as chemical reactivity, thus making it have potential applications in many fields. In the present work, the encapsulation of 13 different Pd_3M (M = Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Pd, Pt, and Au) clusters inside the (10, 0) BNNT has been studied by performing comprehensive density functional theory (DFT) calculations.

1153-1166 **Specificities of boron disubstituted sumanene,** Stevan Armaković, Sanja J. Armaković, Jovan P. Šetrajčić [University of Novi Sad]

In this article we focused on computational research of sumanenes disubstituted by boron where the two carbon atoms are substituted by two boron atoms. Disubstitution of rim carbon atoms with boron atoms significantly affected the geometry of the bowl.

1167-1177 **Molecular dynamics and free energy studies of chirality specificity effects on aminobenzo[a]quinolizine inhibitors binding to DPP-IV,** Cui Wei, Liang Desheng, Gao Jian, Luo Fang, Geng Lingling [Graduate University of the Chinese Academy of Sciences]

See Applications / Ligand binding.

1179-1194 **In vitro inhibitory profile of NDGA against AChE and its in silico structural modifications based on ADME profile,** Chandran Remya, Kalarickal Vijayan Dileep, Ignatius Tintu[Kannur University]

See Applications / Medicinal Chemmistry and Drug Design.

1195-1204 **$B_{30}H_8$, $B_{39}H_9^{2-}$, $B_{42}H_{10}$, $B_{48}H_{10}$, and $B_{72}H_{12}$: polycyclic aromatic snub hydroboron clusters analogous to polycyclic aromatic hydrocarbons,** Hui Bai, Qiang Chen, Ya-Fan Zhao, Yan-Bo Wu, Hai-Gang Lu[Shanxi University]

Calculations performed at the ab initio level using the recently reported planar concentric π-aromatic $B_{18}H_6^{2+}$(**1**) [Chen Q et al. (2011) Phys Chem Chem Phys 13:20620] as a building block suggest the possible existence of a new class of $B_{3n}H_m$ polycyclic aromatic hydroboron (PAHB) clusters—$B_{30}H_8$(**2**), $B_{39}H_9^{2-}$(**3**), $B_{42}H_{10}$(**4/5**), $B_{48}H_{10}$(**6**), and $B_{72}H_{12}$(**7**). The results obtained in this work expand the domain of planar boron-based clusters to a region well beyond B_{20}, and experimental syntheses of these snub $B_{3n}H_m$ clusters through partial hydrogenation of the corresponding bare B_{3n} may open up a new area of boron chemistry parallel to that of PAHCs in carbon chemistry.

1205-1209 **Theoretical study on aluminum carbide endohedral fullerene-$Al_4C@C_{80}$,** Qi Liang Lu, Wen Jun Song, Jun Wei Meng, Jian Guo Wan[Anhui University]

The possibility of a new endohedral fullerene with a trapped aluminum carbide cluster, $Al_4C@C_{80}$-I_h, was theoretical investigated.

1211-1225 **The effect of C-vacancy on hydrogen storage and characterization of H_2 modes on Ti functionalized C_{60} fullerene A first principles study,** Ahmad S. Shalabi, Atef M. El Mahdy, Hayam O. Taha

Density functional theory calculations were performed to examine the effect of a C vacancy on the physisorption of H_2 onto Ti-functionalized C_{60} fullerene when H_2 is oriented along the *x*-, *y*-, and *z*-axes of the fullerene. The effect of the C vacancy on the physisorption modes of H_2 was investigated as a function of H_2 binding energy within the energy window (−0.2 to −0.6 eV) targeted by the Department of Energy (DOE), and as functions of a variety of other physicochemical properties.

1227-1236 **Conformational flexibility of the ErbB2 ectodomain and trastuzumab antibody complex as revealed by molecular dynamics and principal component analysis,** Juan Felipe Franco-Gonzalez, Victor L. Cruz, Javier Ramos[Instituto de Estructura de la Materia,]

See Methodology/ Ligand binding

1237-1250 **Comparison of the structural characteristics of Cu^{2+}-bound and unbound α-syn12 peptide obtained in simulations using different force fields,** Zanxia Cao, Lei Liu, Liling Zhao, Haiyan Li, Jihua Wang[Dezhou University]

The effects of Cu^{2+} binding and the utilization of different force fields when modeling the structural characteristics of α-syn12 peptide were investigated. To this end, we performed extensive temperature replica exchange molecular dynamics (T-REMD) simulations on Cu^{2+}-bound and unbound α-syn12 peptide using the GROMOS 43A1, OPLS-AA, and AMBER03 force fields. Each replica was run for 300 ns

1251-1258 **Effect of varying the 1–4 intramolecular scaling factor in atomistic simulations of long-chain N-alkanes with the OPLS-AA model,** Xianggui Ye, Shengting Cui, Valmor F. de Almeida[University of Tennessee]

A comprehensive molecular dynamics simulation study of n-alkanes using the optimized potential for liquid simulation with all-atoms (OPLS-AA) force field at ambient condition has been performed.

1259-1265 **Boron nitride nanotube based nanosensor for acetone adsorption: a DFT simulation,** Masoud Darvish Ganji, Mahyar Rezvani[Islamic Azad University]

We have investigated the adsorption properties of acetone on zigzag single-walled BNNTs using density functional theory (DFT) calculations. The results obtained show that acetone is strongly bound to the outer surface of a (5,0) BNNT on the top site directly above the boron atom, with a binding energy of −96.16 kJ mol^{-1} and a B–O binding distance of 1.654 Å.

1267-1271 **Influence of transition metals on halogen-bonded complexes of MCCBr···NCH and HCCBr···NCM' (M, M' = Cu, Ag, and Au),** Qiang Zhao, Dacheng Feng[Shandong University]

We have performed quantum chemical calculations for the MCCBr···NCH and HCCBr···NCM' (M, M' = Cu, Ag, and Au) halogen-bonded complexes at the MP2 level.

1273-1283 **Natures of benzene-water and pyrrole-water interactions in the forms of σ and π types: theoretical studies from clusters to liquid mixture,** Wei Gao, Jiqing Jiao, Huajie Feng, Xiaopeng Xuan, Liuping Chen[Sun Yat-sen University]

A combined and sequential use of quantum mechanical (QM) calculations and classical molecular dynamics (MD) simulations was made to investigate the σ and π types of hydrogen bond (HB) in benzene-water and pyrrole-water as clusters and as their liquid mixture, respectively.

1285-1294 **Interaction between shrimp and white spot syndrome virus through PmRab7-VP28 complex: an insight using simulation and docking studies,** Arunima Kumar Verma, Shipra Gupta, Sharad Verma, Abha Mishra, N. S. Nagpure[Indian Council of Agricultural Research]

See Applications / Medicinal Chemmistry and Drug Design.

1295-1299 The role of glycine residues at the C-terminal peptide segment in antinociceptive activity: a molecular dynamics simulation, Yong-Shan Zhao, Rong Zhang, Yang Xu, Yong Cui, Yan-Feng Liu, Yong-Bo Song, Hong-Xing Zhang, Jing-Hai Zhang [Shenyang Pharmaceutical University]

See Applications / Protein Structure Analysis.

1301-1309 **Constant pH molecular dynamics (CpHMD) and molecular docking studies of CquiOBP1 pH-induced ligand releasing mechanism**, Wen-Ting Chu, Ji-Long Zhang,Qing-Chuan Zheng, [Jilin University,]

See Methodology / Ligand binding.

1311-1318 **Effect of superalkali substituents on the strengths and properties of hydrogen and halogen bonds,** Wenkai Tian, Xin Huang, Qingzhong Li[Yantai University,]

Quantum chemical calculations have been performed for the complexes $Li_3OCCX–Y$ (X = Cl, Br, H; Y = NH_3, H_2O, H_2S) and $Li_3OCN–X'Y'$ (X′Y′ = ClF, BrCl, BrF, HF) to study the role of superalkalis in hydrogen and halogen bonds.

1319-1324 **Cytotoxic effect and molecular docking of 4-ethoxycarbonylmethyl-1-(piperidin-4-ylcarbonyl)-thiosemicarbazide—a novel topoisomerase II inhibitor,** Agata Siwek, Paweł Stączek, Monika Wujec, Krzysztof Bielawski,[University of Lodz]

The preliminary cytotoxic effect of 4-ethoxycarbonylmethyl-1-(piperidin-4-ylcarbonyl)-thiosemicarbazide hydrochloride (**1**)—a potent topoisomerase II inhibitor—was measured using a MTT assay.

1325-1338 **Effects of bidentate coordination on the molecular properties rapta-C based complex using t heoretical approach**, Adebayo A. Adeniyi, Peter A. Ajibade[University of Fort Hare]

In this work several quantum properties including the NEDA and QTAIM are computed on three models of rapta-C complexes using DFT with hybrid functional and basis set with ECP and without ECP. Several interesting correlations within the observed properties and also with the reported experimental behaviors of these complexes including their biological activities are presented.

1339-1353 **Electronic structure and decomposition reaction mechanism of cyclopropenone, phenylcylopropenone and their sulfur analogues: a theoretical study,** Shabaan A. K. Elroby, Saadullah G. Aziz, Rifaat Hilal[King Abdulaziz University,]

The electronic structure, the origin of the extraordinary stability and the reaction mechanisms of the decomposition reaction of the three-membered ring cyclopropenone (IO), its phenyl derivative (IIO) and its sulfur analogues (IS and IIS) have been investigated at the B3LYP/6-311 + G** level of theory.

1355-1367 **A solvated ligand rotamer approach and its application in computational protein design,** Xiaoqiang Huang, Ji Yang, Yushan Zhu [Tsinghua University]

See Methodology / Ligand binding.

1369-1377 **New pockets in dengue virus 2 surface identified by molecular dynamics simulation,** Carlos A. Fuzo,Léo Degrève[Universidade de São Paulo]

See Applications / Medicinal Chemmistry and Drug Design.

1379-1389 **Dynamics of DNA polymerase I (Klenow fragment) under external force,** Ping Xie[Key Laboratory of Soft Matter Physics]

See Applications / Nucleic Acids

1391-1397 **Theoretical study of the reaction of CH_2XO (X = F, Cl, Br) radicals with the NO radical,** Yue Li, Hui Zhang, Qingguo Chen, Zesheng Li[Harbin University of Science and Technology]

In this paper, we focus on the multiple-channel reactions of CH_2XO (X = F, Cl, Br) radicals with the NO radical by means of direct dynamic methods. All structures of the stationary points were obtained at the MP2/6-311+G(d,p) level and vibrational frequency analysis was also performed at this level of theory.

Adsorption of three alkaline earth cations inside and outside of a $B_{12}N_{12}$ nano-cage in aqueous medium was investigated using density functional theory. The results obtained are discussed in terms of thermodynamic, geometric, and electronic properties

1451-1458 **Conformational analysis of flephedrone using quantum mechanical models**, Wojciech Kolodziejczyk, Jerzy Jodkowski,Tiffani M. Holmes, Glake A. Hill[Wroclaw Medical University]

Flephedrone is an analogue of cathinone - chemically similar to ephedrine, cathine and other amphetamines. Conformations of all isomers of flephedrone have been studied at the quantum-chemical level.

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1. APPLICATIONS

1.1. *Small Molecules*

Water and solvation

Molecular dynamics of water in the neighborhood of aquaporins

Marcelo Ozu, H. Ariel Alvarez, Andrés N. McCarthy, J. Raúl Grigera ,Osvaldo Chara[Dresden University of Technology]

Euro.biophy. jour., **42**, 223-239, 2013.

Present knowledge obtained by molecular dynamics (MD) simulation studies regarding the dynamics of water, both in the vicinity of biological membranes and within the proteinaceous water channels, also known as aquaporins (AQPs), is reviewed. A brief general summary of the water models most extensively employed in MD simulations (SPC, SPC/E, TIP3P, TIP4P), indicating their most relevant pros and cons, is likewise provided. Structural considerations of water are also discussed, based on different order parameters, which can be extracted from MD simulations as well as from experiments.

A

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Medicinal Chemistry and Drug Design

Substituted indolin-2-ones as p90 ribosomal S6 protein kinase 2 (RSK2) inhibitors: Molecular docking simulation and structure–activity relationship analysis

Ye Zhong, Mengzhu Xue, Xue Zhao, Jun Yuan, Xiaofeng Liu, Jin Huang, Zhenjiang Zhao, Honglin Li, Yufang Xu[China University of Science and Technology]

Bioorg. and Med.Chem., **21**, 1724-1734, 2013.

A series of novel indolin-2-ones inhibitors against p90 ribosomal S6 protein kinase 2 (RSK2) were designed and synthesized and their structure–activity relationship (SAR) was studied. The most potent inhibitor, compound **3s,** exhibited potent inhibition against RSK2 with an IC_{50} value of 0.5 μM and presented a satisfactory selectivity against 23 kinases. The interactions of these inhibitors with RSK2 were investigated based on the proposed binding poses with molecular docking simulation. Four compounds and six compounds exhibited moderate anti-proliferation activities against PC 3 cells and MCF-7 cells, respectively.

Fragment-Based Drug Discovery Using a Multidomain, Parallel MD-MM/PBSA Screening Protocol

Tian Zhu, Hyun Lee, Hao Lei, Christopher Jones, Kavankumar Patel, Michael E. Johnson, and Kirk E. Hevener [University of Illinois at Chicago]

J.Chem. Infor. and Mod. **53**, 560–572, 2013.

We have developed a rigorous computational screening protocol to identify novel fragment-like inhibitors of N^5-CAIR mutase (PurE), a key enzyme involved in de novo purine synthesis that represents a novel target for the design of antibacterial agents. This computational screening protocol utilizes molecular docking, graphics processing unit (GPU)-accelerated molecular dynamics, and Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) free energy estimations to investigate the binding modes and energies of fragments in the active sites of PurE. PurE is a functional octamer comprised of identical subunits.

Bioturbo Similarity Searching: Combining Chemical and Biological Similarity To Discover Structurally Diverse Bioactive Molecules

Anne Mai Wassermann [Novartis Institutes for Biomedical Research Inc], Eugen Lounkine, and Meir Glick

J.Chem. Infor. and Mod. **53**, 692–703, 2013.

Virtual screening using bioactivity profiles has become an integral part of currently applied hit finding methods in pharmaceutical industry. However, a significant drawback of this approach is that it is only applicable to compounds that have been biologically tested in the past and have sufficient activity annotations for meaningful profile comparisons. Although bioactivity data generated in pharmaceutical institutions are growing on an unprecedented scale, the number of biologically annotated compounds still covers only a minuscule fraction of chemical space.

Discovery of subtype selective muscarinic receptor antagonists as alternatives to atropine using in silico pharmacophore modeling and virtual screening methods

Apurba K. Bhattacharjee, James W. Pomponio, Sarah A. Evans, Dmitry Pervitsky, Richard K. Gordon[U.S. Army Medical Research and Material Command]

Bioorg. and Med.Chem., **21**, 2651-2662, 2013.

Muscarinic acetylcholine receptors (mAChRs) have five known subtypes which are widely distributed in both the peripheral and central nervous system for regulation of a variety of cholinergic functions. Atropine is a well known muscarinic subtype non-specific antagonist that competitively inhibits acetylcholine (ACh) at postganglionic muscarinic sites. ACh accumulates due to OP inhibition of acetylcholinesterase (AChE), the enzyme that hydrolyzes Ach. We adopted an in silico pharmacophore modeling strategy to develop features that are characteristics of known M1 subtype-selective compounds and used the model to identify several antagonists by screening an in-house (WRAIR-CIS) compound database.

Medicinal Chemistry and Drug Design (Cont'd)

Pharmacophore modeling, virtual screening, docking and *in silico*ADMET analysis of protein kinase B (PKB β) inhibitors

Vivek K[Nirma University, Ahmedabad]. Vyas ,Manjunath Ghate, Ashutosh Goel

J. Mol.Graph. and Mod., **42,** 7–25 , 2013.

Protein kinase B (PKB) is a key mediator of proliferation and survival pathways that are critical for cancer growth. Therefore, inhibitors of PKB are useful agents for the treatment of cancer. Herein, we describe pharmacophore-based virtual screening combined with docking study as a rational strategy for identification of novel hits or leads. Pharmacophore models of PKB β inhibitors were established using the DISCOtech and refined with GASP from compounds with IC_{50} values ranging from 2.2 to 246 nM.

Pharmacophore modeling, homology modeling, and *in silico*screening reveal mammalian target of rapamycin inhibitory activities for sotalol, glyburide, metipranolol, sulfamethizole, glipizide, and pioglitazone

Mohammad A. Khanfar[a], Majed M. AbuKhader[b], Saja Alqtaishat[a], Mutasem O. Taha[University of Jordan]

J. Mol.Graph. and Mod., **42,** 39–49, 2013.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase and member of the PI3K-related kinase (PIKK) family. It plays a central role in integrating signals from metabolism, energy homeostasis, cell cycle, and stress response. Aberrant PI3K/mTOR activation is commonly observed in diseases such as cancer, diabetes and Alzheimer's disease. Accordingly, we developed common feature binding hypotheses for a set of 6 potent mTOR antagonists. The generated models were validated using receiver operating characteristic (ROC) curve analyses.

A3 adenosine receptor: Homology modeling and 3D-QSAR studies

Anna Maria Almerico [Università degli Studi di Palermo],Marco Tutone, Licia Pantano, Antonino Lauria

J. Mol.Graph. and Mod.,**42,** 60–72, 2013.

S!

Adenosine receptors (AR) belong to the superfamily of G-protein-coupled receptors (GPCRs). They are divided into four subtypes (A1, A2A, A2B, and A3) and can be distinguished on the basis of their distinct molecular structures, distinct tissues distribution, and selectivity for adenosine analogs. The hA3R, the most recently identified adenosine receptor, is involved in a variety of intracellular signaling pathways and physiological functions. Expression of hA3R was reported to be elevated in cancerous tissues and A3 antagonists could be proposed for therapeutic treatments of tumor.

Insights into the structural determinants for selective inhibition of nitric oxide synthase isoforms

Bruno L. Oliveira, Irina S. Moreira, Pedro A. Fernandes, Maria J. Ramos, Isabel Santos, João D. G. Correia[Universidade Técnica de Lisboa]

J. Mol.Mod., **19,** 1537-1551, 2013.

A!

Selective inhibition of the nitric oxide synthase isoforms (NOS) is a promising approach for the treatment of various disorders. However, given the high active site conservation among all NOS isoforms, the design of selective inhibitors is a challenging task. Analysis of the X-ray crystal structures of the NOS isoforms complexed with known inhibitors most often gives no clues about the structural determinants behind the selective inhibition since the inhibitors share the same binding conformation. Aimed at a better understanding of the structural factors responsible for selective inhibition of NOS isoforms we have performed MD simulations for iNOS, nNOS and eNOS complexed with N^{ω}-NO_2-L-Arg (**1**), and with the aminopyridine derivatives **2** and **3**.

Medicinal Chemistry and Drug Design (Cont'd)

Pharmacophoric features of drugs with guanylurea moiety: an electronic structure analysis

Yoganjaneyulu Kasetti, Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Mod., **19,** 1865-1874, 2013.

Several therapeutically important compounds contain guanylurea (GU) moiety. The appropriate tautomeric state of these species has not been explored, preliminary studies indicated that the traditional representation of this class of compounds use a high energy tautomeric state. In this work, quantum chemical studies (HF, B3LYP, MP2, G2MP2 and CBS-Q methods) were performed on the medicinally important GU based drugs so as to identify their stable tautomeric state and to understand the pharmacophoric features of these drugs.

Comparative modeling of Rab6 proteins: identification of key residues and their interactions with guanine nucleotides

Sandeep Kumar Mulukala Narasimha[Osmania University], Shravan Kumar Gunda, Mahmood Shaik

J. Mol.Mod., **19,** 1891-1900 , 2013

A!

The cytoplasm of a eukaryotic cell consists of a wide variety of membrane bound cell organelles and continuous flow of proteins amongst these organelles is a major challenge and must be stringently maintained in order to continue the correct biochemical functioning inside a cell. In this paper we put forth the homology modeling and docking studies of Rab6A proteins (*Mus musculus*, *Gallus gallus* and *Caenorhabditis elegans*) with GTP, GMP-PNP and GDP molecules and a comparative study between these proteins is done to identify key residues out of which serine of the phosphate binding loop (P – loop) and aspartic acid showed prominent interactions with the GTP, GDP and GMP-PNP nucleotides and cogitate that aspartic acid might also help in the stabilization of the switch I region of the Rab proteins besides serine.

Molecular Mechanism of the Inhibition of EGCG on the Alzheimer $A\beta_{1-42}$ Dimer

Tong Zhang, Jian Zhang, Philippe Derreumaux, and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B., **117**, 3993-4002, 2013**.**

A!

Growing evidence supports that amyloid β (Aβ) oligomers are the major causative agents leading to neural cell death in Alzheimer's disease. The polyphenol (−)-epigallocatechin gallate (EGCG) was recently reported to inhibit Aβ fibrillization and redirect Aβ aggregation into unstructured, off-pathway oligomers. Given the experimental challenge to characterize the structures of Aβ/EGCG complexes, we performed extensive atomistic replica exchange molecular dynamics simulations of $A\beta_{1-42}$ dimer in the present and absence of EGCG in explicit solvent.

Host-Guest Systems

Ligand Binding Site Identification by Higher Dimension Molecular Dynamics

Achani K. Yatawara, Milan Hodoscek, and Dale F. Mierke [Dartmouth College]

J.Chem. Infor. and Mod. **53**, 674–680, 2013.

A!

We propose a new molecular dynamics (MD) protocol to identify the binding site of a guest within a host. The method utilizes a four spatial (4D) dimension representation of the ligand allowing for rapid and efficient sampling within the receptor. We applied the method to two different model receptors characterized by diverse structural features of the binding site and different ligand binding affinities. The Abl kinase domain is comprised of a deep binding pocket and displays high affinity for the two chosen ligands examined here.

Carbon Nanoparticles

Silicon–doping in carbon nanotubes: formation energies, electronic structures, and chemical reactivity

Ruixin Bian, Jingxiang Zhao, Honggang Fu [Heilongjiang University]

J. Mol.Mod., **19,** 1667-1675, 2013.

By carrying out density functional theory (DFT) calculations, we have studied the effects of silicon (Si)-doping on the geometrical and electronic properties, as well as the chemical reactivity of carbon nanotubes (CNTs). It is found that the formation energies of these nanotubes increase with increasing tube diameters, indicating that the embedding of Si into narrower CNTs is more energetically favorable. For the given diameters, Si-doping in a (*n*, 0) CNT is slightly easier than that of in (*n*, *n*) CNT. Moreover, the doped CNTs with two Si atoms are easier to obtain than those with one Si atom.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

Message passing interface and multithreading hybrid for parallel molecular docking of large databases on petascale high performance computing machines

Xiaohua Zhang, Sergio E. Wong, Felice C. Lightstone[Lawrence Livermore National Lab]

J. Comp. Chem., **34**, 915–927, 2013.

S!

A mixed parallel scheme that combines message passing interface (MPI) and multithreading was implemented in the AutoDock Vina molecular docking program. The resulting program, named VinaLC, was tested on the petascale high performance computing (HPC) machines at Lawrence Livermore National Laboratory. To exploit the typical cluster-type supercomputers, thousands of docking calculations were dispatched by the master process to run simultaneously on thousands of slave processes, where each docking calculation takes one slave process on one node, and within the node each docking calculation runs via multithreading on multiple CPU cores and shared memory.

Bioinformatics and Cheminformatics (Cont'd)

An *in silico* method for designing thermostable variant of a dimeric mesophilic protein based on its 3D structure

Sohini Basu, Srikanta Sen[Molecular Modeling Group, Biolab, Chembiotek, TCG Lifesciences]

J. Mol.Graph. and Mod.,**42,** 92–103 2013.

A!

Designing proteins with enhanced thermostability has been a major interest of protein engineering because of its potential industrial applications. Here, we have presented a computational method for designing dimeric thermostable protein based on rational mutations on a mesophilic protein. Experimental and structural data indicate that the surface stability of a protein is a major factor controlling denaturation of a protein and ion-pairs are most efficient in enhancing the stability of the surfaces of the monomers and the interface between them.

Improving ranking of models for protein complexes with side chain modeling and atomic potentials

Shruthi Viswanath, D. V. S. Ravikant and Ron Elber[University of Texas at Austin]

Proteins: Stru. Fun. & Bioinf., **81**, 592–606, 2013.

A!

An atomically detailed potential for docking pairs of proteins is derived using mathematical programming. A refinement algorithm that builds atomically detailed models of the complex and combines coarse grained and atomic scoring is introduced. The refinement step consists of remodeling the interface side chains of the top scoring decoys from rigid docking followed by a short energy minimization. The refined models are then re-ranked using a combination of coarse grained and atomic potentials.

LabCaS: Labeling calpain substrate cleavage sites from amino acid sequence using conditional random fields

Yong-Xian Fan, Yang Zhang[University of Michigan] and Hong-Bin Shen

Proteins: Stru. Fun. & Bioinf., **81**, 622–634, 2013.

The calpain family of Ca^{2+}-dependent cysteine proteases plays a vital role in many important biological processes which is closely related with a variety of pathological states. Activated calpains selectively cleave relevant substrates at specific cleavage sites, yielding multiple fragments that can have different functions from the intact substrate protein. In this work, we aim to develop a new computational approach (LabCaS) for accurate prediction of the calpain substrate cleavage sites from amino acid sequences.

Protein Confirmational Analysis

The role of salt concentration and magnesium binding in HIV-1 subtype-A and subtype-B kissing loop monomer structures

Taejin Kim & Bruce A. Shapiro**[**Frederick National Laboratory for Cancer Research]

J. Biomol. Stru. and Dyn., **31**, 495-510, 2013.

The subtype-B monomers of the human immunodeficiency virus type-1 (HIV-1) have experimentally been shown to dimerize at high salt concentration or in the presence of magnesium, while the dimerization of the subtype-A monomers requires magnesium binding at the G_{273} or G_{274} phosphate groups regardless of salt concentration. We used explicit solvent molecular dynamics (MD) simulations to investigate the conformational changes in subtype-A and -B monomers in different salt concentrations, and we found that our MD simulation results are consistent with those of experiments.

Protein Confirmational Analysis (Cont'd)

Ligand Binding Pathway Elucidation for Cryptophane Host–Guest Complexes

Christopher C. Roberts and Chia-en A. Chang [University of California]

J. Chem. Theor. and Comp, **9**, 2010–2019, 2013.

Modeling binding pathways can provide insight into molecular recognition, including kinetic mechanisms, barriers to binding, and gating effects. This work represents a novel computational approach, Hopping Minima, for the determination of conformational transitions of single molecules as well as binding pathways for molecular complexes. The method begins by thoroughly sampling a set of conformational minima for a molecular system. The natural motions of the system are modeled using the normal modes of the sampled minima.

Protein Structure Analysis

Structure-based redesign of proteins for minimal T-cell epitope content

Yoonjoo Choi, Karl E. Griswold, Chris Bailey-Kellogg [Dartmouth College]

J. Comp. Chem., **34**, 879–891, 2013.

S!

The protein universe displays a wealth of therapeutically relevant activities, but T-cell driven immune responses to non-"self" biological agents present a major impediment to harnessing the full diversity of these molecular functions. Mutagenic T-cell epitope deletion seeks to mitigate the immune response, but can typically address only a small number of epitopes. Here, we pursue a "bottom-up" approach that redesigns an entire protein to remain native-like but contain few if any immunogenic epitopes.

Protein Dynamics

Confinement-Dependent Friction in Peptide Bundles

Aykut Erbaş[Free University of Berlin], Roland R. Netz

Biophysical Journal. **104**, 1285-1295, 2013.

Friction within globular proteins or between adhering macromolecules crucially determines the kinetics of protein folding, the formation, and the relaxation of self-assembled molecular systems. One fundamental question is how these friction effects depend on the local environment and in particular on the presence of water. In this model study, we use fully atomistic MD simulations with explicit water to obtain friction forces as a single polyglycine peptide chain is pulled out of a bundle of *k* adhering parallel polyglycine peptide chains.

Protein Dynamics (Cont'd)

Low-temperature molecular dynamics simulations of horse heart cytochrome c and comparison with inelastic neutron scattering data

Wojciech Pulawski, Slawomir Filipek, Anna Zwolinska, Aleksander Debinski,Krystiana Krzysko,RamónGarduñoJuárez, SowmyaViswanathan, VenkatesanRenugopalakrishnan [Northeastern University]

Euro.biophy. jour., **42**, 291-300, 2013.

A

Molecular dynamics (MD) simulation combined with inelastic neutron scattering can provide information about the thermal dynamics of proteins, especially the low-frequency vibrational modes responsible for large movement of some parts of protein molecules. We performed several 30-ns MD simulations of cytochrome c (Cyt c) in a water box for temperatures ranging from 110 to 300 K and compared the results with those from experimental inelastic neutron scattering. The low-frequency vibrational modes were obtained via dynamic structure factors, $S(Q, \omega)$, obtained both from inelastic neutron scattering experiments and calculated from MD simulations for Cyt c in the same range of temperatures.

Effect of Solvent on the Self-Assembly of Dialanine and Diphenylalanine Peptides

Anastassia N. Rissanou, Evangelos Georgilis, Emmanouil Kasotakis, Anna Mitraki, and Vagelis Harmandaris [University of Crete]

J. Phys. Chem. B., **117**, 3962–3975, 2013**.**

Diphenylalanine (FF) is a very common peptide with many potential applications, both biological and technological, due to a large number of different nanostructures which it attains. The current work concerns a detailed study of the self-assembled structures of FF in two different solvents, an aqueous (H_2O) and an organic (CH_3OH) through simulations and experiments. Detailed atomistic molecular dynamics (MD) simulations of FF in both solvents have been performed, using an explicit solvent model.

Study of the aggregation mechanism of polyglutamine peptides using replica exchange molecular dynamics simulations

Miki Nakano, Kuniyoshi Ebina, Shigenori Tanaka [Kobe University]

J. Mol.Mod., **19,** 1627-1639, 2013.

Polyglutamine (polyQ, a peptide) with an abnormal repeat length is the causative agent of polyQ diseases, such as Huntington's disease. Although glutamine is a polar residue, polyQ peptides form insoluble aggregates in water, and the mechanism for this aggregation is still unclear. To elucidate the detailed mechanism for the nucleation and aggregation of polyQ peptides, replica exchange molecular dynamics simulations were performed for monomers and dimers of polyQ peptides with several chain lengths.

Observed Mechanism for the Breakup of Small Bundles of Cellulose Iα and Iβ in Ionic Liquids from Molecular Dynamics Simulations

Brooks D. Rabideau, Animesh Agarwal, and Ahmed E. Ismail [RWTH Aachen University]

J. Phys. Chem. B., **117**, 3469–3479, 2013**.**

Explicit, all-atom molecular dynamics simulations are used to study the breakup of small bundles of cellulose Iα and Iβ in the ionic liquids [BMIM]Cl, [EMIM]Ac, and [DMIM]DMP. In all cases, significant breakup of the bundles is observed with the initial breakup following a common underlying mechanism. Anions bind strongly to the hydroxyl groups of the exterior strands of the bundle, forming negatively charged complexes.

Protein Dynamics (Cont'd)

Targeted molecular dynamics (TMD) of the full-length KcsA potassium channel: on the role of the cytoplasmic domain in the opening process

Yan Li, Florent Barbault, Michel Delamar[Univ Paris Diderot, Sorbonne Paris Cité], Ruisheng Zhang, Rongjing Hu

J. Mol.Mod., **19,** 1651-1666 , 2013.

Some recent papers clearly indicate that the cytoplasmic domain of KcsA plays a role in pH sensing. We have performed, for the first time, a targeted molecular dynamics (TMD) simulation of the opening of full-length KcsA at pH 4 and pH 7, with a special interest for the cytoplasmic domain. Association energy calculations show a stabilization at pH 7 confirming that the protonation of some amino-acids at pH 4 in this domain plays a role in the opening process. A careful analysis of the pH dependent charges borne by residues in the cytoplasmic domain and their interactions confirms some literature experimental data and permits to give further insight into the role played by some of them in the opening process.

Conformation and Dynamics of a Cyclic Disulfide-Bridged Peptide: Effects of Temperature and Solvent

Fee Li, Kenny Bravo-Rodriguez, Charlotte Phillips, Rüdiger W. Seidel, Florian Wieberneit, Raphael Stoll, Nikos L. Doltsinis, Elsa Sanchez-Garcia, and Wolfram Sander [Ruhr-Universität Bochum]

J. Phys. Chem. B., **117**, 3560–3570, 2013**.**

The cyclic disulfide-bridged tetrapeptide cyclo(Boc-Cys-Pro-Gly-Cys-OMe) (**1**) was designed as a model for the study of solvent-driven conformational changes in peptides. The three-dimensional structure and dynamics of **1** were studied using a variety of experimental and computational techniques. The crystal structure of **1** reveals a β-turn stabilized by a hydrogen bond between the two cysteine residues. In solution, the UV–CD and NMR analysis of **1** suggest a β-turn II conformation, stable up to 60 °C.

The intrinsic stability of the human prion β-sheet region investigated by molecular dynamics

Alfonso De Simone, Francesca Stanzione, Daniela Marasco, Luigi Vitagliano & Luciana Esposito [Istituto di Biostrutture e Bioimmagini]

J. Biomol. Stru. and Dyn., **31**, 441-452, 2013.

Human prion diseases are neurodegenerative disorders associated to the misfolding of the prion protein (PrP). Common features of prion disorders are the fibrillar amyloid deposits and the formation of prefibrillar oligomeric species also suggested as the origin of cytotoxicity associated with diseases. Although the process of PrP misfolding has been extensively investigated, many crucial aspects of this process remain unclear. We have here carried out a molecular dynamics study to evaluate the intrinsic dynamics of PrP β-sheet, a region that is believed to play a crucial role in prion aggregation

S

Effects of Confinement on the Structure and Dynamics of an Intrinsically Disordered Peptide: A Molecular-Dynamics Study

J. Srinivasa Rao and Luis Cruz [Drexel University]

J. Phys. Chem. B., **117**, 3707–3719, 2013

In vivo, proteins and peptides are exposed to radically different environments than those in bulk. Because of the abundance of other cellular components, proteins perform their function in crowded and confined spaces. Confinement has been shown to alter the structure, dynamics, and folding of proteins that possess a native fold. Little is known, however, of the effects of confinement on biologically important intrinsically disordered proteins or peptides (IDP). Here, we use extensive MD simulations to investigate the effects of confinement in an IDP, the $A\beta_{21–30}$, a central folding nucleus of the full length amyloid β-protein.

Ligand Binding/Docking

Affinity maturation of antiHER2 monoclonal antibody MIL5 using an epitope-specific synthetic phage library by computational design

Chunxia Qiao, Ming Lv, Xinying Li, Jing Geng, Yan Li, Jiyan Zhang, Zhou Lin, Jiannan Feng & Beifen Shen [Institute of Basic Medical Sciences,]

J. Biomol. Stru. and Dyn., **31**, 511-521, 2013.

Increased affinities mainly equal to improved biological efficacy in many cases. By now, display methods including phage library are widely exploited to obtain higher affinity antibodies. Traditional library methods mainly focus on complementary determining region mutagenesis, in which extensive screening of variant combinations as well as large library capacity is required to find higher affinity clones. In this study, based on the modeling 3D complex structure of antigen (HER2)–antibody (MIL5) complex, the key residues of contact surface were predicted and identified to guide the synthetic phage library design.

New Insights on the Molecular Recognition of Imidacloprid with *Aplysia californica* AChBP: A Computational Study

José P. Cerón-Carrasco, Denis Jacquemin, Jérôme Graton, Steeve Thany, and Jean-Yves Le Questel [Université de Nantes]

J. Phys. Chem. B., **117**, 3944–3953, 2013**.**

The binding of imidacloprid (IMI), the forerunner of neonicotinoid insecticides, with the acetylcholine binding protein (AChBP) from *Aplysia californica*, the established model for the extracellular domain of insects nicotinic acetylcholine receptors, has been studied with a two-layer ONIOM partition approach (M06-2X/6-311G(d):PM6). Our calculations allow delineating the contributions of the key residues of AChBP for IMI binding. In particular, the importance of Trp147 and Cys190–191, through weak CH···π interactions and both van der Waals and hydrogen-bond (H-bond) interactions, respectively, are highlighted.

FEW: A workflow tool for free energy calculations of ligand binding

Nadine Homeyer, Holger Gohlke[Heinrich-Heine-University]

J. Comp. Chem., **34**, 965–973, 2013.

In the later stages of drug design projects, accurately predicting relative binding affinities of chemically similar compounds to a biomolecular target is of utmost importance for making decisions based on the ranking of such compounds. So far, the extensive application of binding free energy approaches has been hampered by the complex and time-consuming setup of such calculations. We introduce the free energy workflow (FEW) tool that facilitates setup and execution of binding free energy calculations with the AMBER suite for multiple ligands.

Ligand Binding / Docking (Cont'd)

Computational study and peptide inhibitors design for the CDK9 – cyclin T1 complex

Jelena Randjelović, Slavica Erić[University of Belgrade], Vladimir Savić

J. Mol.Mod., **19,** 1711-1725, 2013.

A!

Cyclin dependent kinase 9 (CDK9) is a protein that belongs to the cyclin-dependent kinases family, and its main role is in the regulation of the cell transcription processes. Since the increased activity of CDK9 is connected with the development of pathological processes such as tumor growth and survival and HIV-1 replication, inhibition of the CDK9 could be of particular interest for treating such diseases. The activation of CDK9 is initiated by the formation of CDK9/cyclin T1 complex, therefore disruption of its formation could be a promising strategy for the design of CDK9 inhibitors.

Homology model of nonmuscle myosin heavy chain IIA and binding mode analysis with its inhibitor blebbistatin

Yanni Lv, Shuai Lu, Tao Lu, Junping Kou, Boyang Yu [China Pharmaceutical University]

J. Mol.Mod., **19,** 1801-1810, 2013.

S!

Nonmuscle myosin heavy chain IIA (NMMHC IIA, gene code: MYH9) plays a critical role in physiological and pathological functions. A homology model of NMMHC IIA was constructed based on the crystal structure of smooth muscle myosin II. Blebbistatin, a myosin II ATPase inhibitor, had been found to bind to NMMHC IIA with Leu228 as the important amino acid residue and van der Waals contacts as the main force of the interaction. The final complex demonstrated that the destruction of the salt bridge occurred between the Arg204 and Glu427 residues when blebbistatin was present.

Computational design of glutamate dehydrogenase in *Bacillus subtilis* natto

Li-Li Chen, Jia-Le Wang, Yu Hu, Bing-Jun Qian, Xiao-Min Yao, Jing-Fang Wang, Jian-Hua Zhang[Shanghai Jiao Tong University]

J. Mol.Mod., **19,** 1919-1927 , 2013.

Bacillus subtilis natto is widely used in industry to produce natto, a traditional and popular Japanese soybean food. However, during its secondary fermentation, high amounts of ammonia are released to give a negative influence on the flavor of natto. Glutamate dehydrogenase (GDH) is a key enzyme for the ammonia produced and released, because it catalyzes the oxidative deamination of glutamate to alpha-ketoglutarate using NAD^+ or $NADP^+$ as co-factor during carbon and nitrogen metabolism processes. To solve this problem, we employed multiple computational methods model and re-design GDH from *Bacillus subtilis* natto.

Ligand Binding / Docking (Cont'd)

Interactions of selected indole derivatives with phospholipase A_2: *in silico and in vitro* analysis

Kalarickal Vijayan Dileep, Chandran Remya, Ignatius Tintu,Madathilkovilakathu Haridas, Chittalakkottu Sadasivan [Kannur University]

J. Mol.Mod., **19,** 1811-1817, 2013.

Phospholipase A2 (PLA_2) is one of the key enzymes involved in the formation of inflammatory mediators. Inhibition of PLA_2 is considered to be one of the efficient methods to control inflammation. *In silico* docking studies of 160 selected indole derivatives performed against porcine pancreatic PLA_2 ($ppsPLA_2$) suggested that, CID2324681, CID8617 (indolebutyric acid or IBA), CID22097771 and CID802 (indoleacetic acid or IAA) exhibited highest binding energies. *In silico* analysis was carried out to predict some of the ADME properties. The binding potential of these compounds with human non pancreatic secretory PLA_2 ($hnpsPLA_2$) was determined using molecular docking studies.

Enzyme Catalysis

Theoretical study on the degradation of ADP-ribose polymer catalyzed by poly(ADP-ribose) glycohydrolase

Qianqian Hou[a], Xin Hu[b], Xiang Sheng[a] ,Yongjun Liu [Shandong University], ,Chengbu Liu[a]

J. Mol.Graph. and Mod., **42,** 26–31, 2013.

Poly(ADP-ribose) glycohydrolase (PARG) is the only enzyme responsible for the degradation of ADP-ribose polymers. Very recently, the first crystal structure of PARG was reported (Dea Slade, et al., Nature 477 (2011) 616), and a possible S_N1-type-like mechanism was proposed. In this work, we present a computational study on the hydrolysis of glycosidic ribose–ribose bond catalyzed by PARG using hybrid density functional theory (DFT) methods. Based on the crystal structure of PARG, three models of the active site were constructed.

Unraveling the Role of the Protein Environment for [FeFe]-Hydrogenase: A New Application of Coarse-Graining

Martin McCullagh and Gregory A. Voth [The University of Chicago]

J. Phys. Chem. B., **117**, 4062-4071, 2013**.**

A!

Hydrogenase enzymes are natural biocatalysts that might be harnessed to reduce the cost of hydrogen gas production. [FeFe]-hydrogenases are the most effective of three such enzymes at catalyzing H^+ reduction. In this study, we develop and apply a novel combination of all-atom molecular dynamics and coarse-grained (CG) analysis to characterize two important steps of the catalytic cycle of [FeFe]-hydrogenase. The first is the electron transport through FeS clusters to the active site.

Protein-Protein Interactions

Conformational Contribution to Thermodynamics of Binding in Protein-Peptide Complexes through Microscopic Simulation

Amit Das, J. Chakrabarti, Mahua Ghosh[Biological and Macromolecular Sciences Kolkata]

Biophysical Journal. **104**, 1274-1284, 2013.

A

We extract the thermodynamics of conformational changes in biomacromolecular complexes from the distributions of the dihedral angles of the macromolecules. These distributions are obtained from the equilibrium configurations generated via all-atom molecular dynamics simulations. The conformational thermodynamics data we obtained for calmodulin-peptide complexes using our methodology corroborate well with the experimentally observed conformational and binding entropies. The conformational free-energy changes and their contributions for different peptide-binding regions of calmodulin are evaluated microscopically

Mapping Monomeric Threading to Protein–Protein Structure Prediction

Aysam Guerler, Brandon Govindarajoo, and Yang Zhang [University of Michigan]

J.Chem. Infor. and Mod. **53**, 717-725, 2013.

The key step of template-based protein–protein structure prediction is the recognition of complexes from experimental structure libraries that have similar quaternary fold. Maintaining two monomer and dimer structure libraries is however laborious, and inappropriate library construction can degrade template recognition coverage. We propose a novel strategy SPRING to identify complexes by mapping monomeric threading alignments to protein–protein interactions based on the original oligomer entries in the PDB, which does not rely on library construction and increases the efficiency and quality of complex template recognitions.

Rational design of the survivin/CDK4 complex by combining protein–protein docking and molecular dynamics simulations

Jana Selent, Agnieszka A. Kaczor, Ramon Guixà-González, Pau Carrió, Manuel Pastor, Cristian Obiol-Pardo [IMIM/Universitat Pompeu Fabra,]

J. Mol.Mod., **19,** 1507-1514, 2013.

A!

Survivin, the smallest inhibitor of apoptosis protein (IAP), is a valid target for cancer research. It mediates both the apoptosis pathway and the cell cycle and has been proposed to form a complex with the cyclin-dependent kinase protein CDK4. The resulting complex transports CDK4 from the cytosol to the nucleus, where CDK4 participates in cell division. Survivin has been recognized as a node protein that interacts with several partners; disruption of the formed complexes can lead to new anticancer compounds. We propose a rational model of the survivin/CDK4 complex that fulfills the experimental evidence and that can be used for structure-based design of inhibitors modifying its interface recognition.

Membrane Proteins and Lipid Peptide Interactions

The Association of Polar Residues in the DAP12 homodimer: TOXCAT and Molecular Dynamics Simulation Studies

Peng Wei, Bo-Kai Zheng, Peng-Ru Guo, Toru Kawakami, Shi-Zhong Luo[University of Chemical Technology]
Biophysical Journal. **104**, 1435-1444, 2013.

A

Dimerization of the transmembrane (TM) adaptor protein DAP12 plays a key role in mediating activation signals through TM-TM association with cell-surface receptors. Herein, we apply the TOXCAT assay and molecular dynamics simulation to analyze dynamics and dimerization of the TM helix of DAP12 in the membrane bilayer. In the TOXCAT assay, we performed site-specific mutagenesis of potential dimerization motifs in the DAP12 TM domain.

The Effect of Sterols on Amphotericin B Self-Aggregation in a Lipid Bilayer as Revealed by Free Energy Simulations

Anna Neumann, Maciej Baginski, Szymon Winczewski, Jacek Czub[Gdansk University of Technolog]

Biophysical Journal. **104**, 1485-1494, 2013.

A

Amphotericin B (AmB) is an effective but toxic antifungal drug, known to increase the permeability of the cell membrane, presumably by assembling into transmembrane pores in a sterol-dependent manner. The aggregation of AmB molecules in a phospholipid bilayer is, thus, crucial for the drug's activity. To provide an insight into the molecular nature of this process, here, we report an atomistic molecular dynamics simulation study of AmB head-to-head dimerization in a phospholipid bilayer, a possible early stage of aggregation.

Proline Facilitates Membrane Insertion of the Antimicrobial Peptide Maculatin 1.1 via Surface Indentation and Subsequent Lipid Disordering

David I. Fernandez, Tzong-Hsien Lee, Marc-Antoine Sani, Marie-Isabel Aguilar, Frances Separovic[University of Melbourne]

Biophysical Journal. **104**, 1495-1507, 2013.

The role of proline in the disruption of membrane bilayer structure upon antimicrobial peptide (AMP) binding was studied. Specifically, ^{31}P and ^{2}H solid-state NMR and dual polarization interferometry (DPI) were used to analyze the membrane interactions of three AMPs: maculatin 1.1 and two analogs in which Pro-15 is replaced by Gly and Ala. For NMR, deuterated dimyristoylphosphatidylcholine (d_{54}-DMPC) and d_{54}-DMPC/dimyristoylphosphatidylglycerol (DMPG) were used to mimic eukaryotic and prokaryotic membranes, respectively. In fluid-phase DMPC bilayer systems, the peptides interacted primarily with the bilayer surface, with the native peptide having the strongest interaction

Membrane protein native state discrimination by implicit membrane models

Olga Yuzlenko, Themis Lazaridis [City College of the City University of New York]

J. Comp. Chem., **34**, 731–738, 2013.

A!

Four implicit membrane models [IMM1, generalized Born (GB)-surface area-implicit membrane (GBSAIM), GB with a simple switching (GBSW), and heterogeneous dielectric GB (HDGB)] were tested for their ability to discriminate the native conformation of five membrane proteins from 450 decoys generated by the Rosetta-Membrane program. The energy ranking of the native state and *Z*-scores were used to assess the performance of the models.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

TargetATPsite: A template-free method for ATP-binding sites prediction with residue evolution image sparse representation and classifier ensemble

Dong-Jun Yu, Jun Hu, Yan Huang,Hong-Bin Shen [Shanghai Jiao Tong University], Yong Qi[1,2], Zhen-Min Tang[1], Jing-Yu Yang[1]

J. Comp. Chem., **34**, 974–985, 2013.

Understanding the interactions between proteins and ligands is critical for protein function annotations and drug discovery. We report a new sequence-based template-free predictor (TargetATPsite) to identify the Adenosine-5′-triphosphate (ATP) binding sites with machine-learning approaches. Two steps are implemented in TargetATPsite: binding residues and pockets predictions, respectively. To predict the binding residues, a novel image sparse representation technique is proposed to encode residue evolution information treated as the input features.

The Effects of Cryosolvents on DOPC−β-Sitosterol Bilayers Determined from Molecular Dynamics Simulations

Zak E. Hughes, Chris J. Malajczuk, and Ricardo L. Mancera [Curtin University]

J. Phys. Chem. B., **117**, 3362–3375, 2013**.**

Polyhydroxylated alcohols and DMSO are common cryosolvents that can damage cell membranes at sufficiently high concentrations. The interaction of representative plant cell membranes composed of mixed 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC)-β-sitosterol bilayers, at a range of compositions, with a variety of cryosolvent molecules (DMSO, propylene glycol, ethylene glycol, glycerol, and methanol) has been investigated using molecular dynamics simulations.

Phase Separation in a Lipid/Cholesterol System: Comparison of Coarse-Grained and United-Atom Simulations

Davit Hakobyan and Andreas Heuer [Institute of Physical Chemistry]

J. Phys. Chem. B., **117**, 3841–3851, 2013**.**

Ternary mixtures of saturated and unsaturated phospholipids and cholesterol constitute a well-known model system to study raft formation in membranes. This phenomenon is, e.g., observed in cell membranes. Here, coarse-grained (CG) and microscopic united-atom (UA) simulations are performed to investigate the phase separation of a membrane bilayer for the ternary system of saturated 16:0 (DPPC) and unsaturated 18:2 (DUPC) phospholipids and cholesterol (CHOL). The results of a 9 μs UA simulation demonstrate the onset of phase separation and can be compared with properties of the corresponding CG system

Predictions of Phase Separation in Three-Component Lipid Membranes by the MARTINI Force Field

Ryan S. Davis , P. B. Sunil Kumar , Maria Maddalena Sperotto , Mohamed Laradji [The University of Memphis]

J. Phys. Chem. B., **117**, 4072–4080, 2013**.**

The phase behavior of the coarse-grained MARTINI model for three-component lipid bilayers composed of dipalmytoyl-phosphatidylcholine (DPPC), cholesterol (Chol), and an unsaturated phosphatidylcholine (PC) was systematically investigated by molecular dynamics simulations. The aim of this study is to understand which types of unsaturated PC induce the formation of thermodynamically stable coexisting phases when added to mixtures of DPPC and Chol and to unravel the mechanisms that drive phase separation in such three-component mixtures

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Lipid a from lipopolysaccharide recognition: Structure, dynamics and cooperativity by molecular dynamics simulations

Jose Antonio Garate and Chris Oostenbrink[University of Natural Resources and Life Sciences]

Proteins: Stru. Fun. & Bioinf., **81**, 658–674, 2013.

A!

Molecular dynamics simulations of Lipid A and its natural precursor Lipid IVA from *E.coli* have been carried out free in solution, bound to the myeliod differentiation protein 2 (MD2) and in the complex of MD2 with the toll like receptor 4 (TLR4). In addition, simulations of the ligand free MD2 and MD2-TLR4 complex were performed. A structural and energetic characterization of the bound and unbound states of Lipid A/IVA was generated. As the crystal structures depict, the main driving force for MD2-Lipid A/IVA are the hydrophobic interactions between the aliphatic tails and the MD2 cavity. The charged phosphate groups do strongly interact with positively charged residues, located at the surface of MD2.

Protein Folding

The Prolyl Isomerase SlyD Is a Highly Efficient Enzyme but Decelerates the Conformational Folding of a Client Protein

Gabriel Zoldák, Anne-Juliane Geitner, and Franz X. Schmid [Universität Bayreuth]

J. Am. Chem. Soc., 2013, **135**,4372–4379

Folding enzymes often use distinct domains for the interaction with a folding protein chain and for the catalysis of intrinsically slow reactions such as prolyl *cis*/*trans* isomerization. Here, we investigated the refolding reaction of ribonuclease T1 in the presence of the prolyl isomerase SlyD from *Escherichia coli* to examine how this enzyme catalyzes the folding of molecules with an incorrect *trans* proline isomer and how it modulates the conformational folding of the molecules with the correct *cis* proline.

Native States of Fast-Folding Proteins Are Kinetic Traps

Alex Dickson and Charles L. Brooks, III [The University of Michigan]

J. Am. Chem. Soc., 2013, **135**, 4729–4734

A

It has been suggested that the native state of a protein acts as a kinetic hub that can facilitate transitions between nonnative states. Using recently developed tools to quantify mediation probabilities ("hub scores"), we quantify hub-like behavior in atomic resolution trajectories for the first time. We use a data set of trajectory ensembles for 12 fast-folding proteins previously published by D. E. Shaw Research (Lindorff-Larsen, K.; et al. How Fast-Folding Proteins Fold. *Science***2011**, *334*, 517) with an aggregate simulation time of over 8.2 ms. We visualize the free-energy landscape of each molecule using configuration space networks, and show that dynamic quantities can be qualitatively understood from visual inspection of the networks.

Protein-Nucleic acid Interactions

Study of DNA base-Li doped SiC nanotubes in aqueous solutions: a computer simulation study

Sepideh Ketabi[Islamic Azad University], Seyed Majid Hashemianzadeh, Morteza MoghimiWaskasi

J. Mol.Mod., **19,** 1605-1615, 2013.

Due to the importance of soluble nanotubes in biological systems, computational research on DNA base functionalized nanotubes is of interest. This study presents the quantitative results of Monte Carlo simulations of Li-doped silicon carbide nanotubes and its nucleic acid base complexes in water. Each species was first modeled by quantum mechanical calculations and then Monte Carlo simulations were applied to study their properties in aqueous solution.

Nucleic Acids

Structural and energetic insights into sequence-specific interaction in DNA–drug recognition: development of affinity predictor and analysis of binding selectivity

Jingheng Ning[Jiangsu University], Weiwei Chen, Jiaojiao Li, Zaixi Peng, Jianhui Wang, Zhong Ni

J. Mol.Mod., **19,** 1573-1582 , 2013.

S!

Although the molecular mechanism and thermodynamic profile of a wide variety of chemical agents have been examined intensively in the past decades in terms of specific recognition of their protein receptors, to date the physicochemical nature of DNA–drug recognition and association still remains largely unexplored. The present study focused on understanding the structural basis, energetic landscape, and biological implications underlying the binding of small-molecule ligands to their cognate or non-cognate DNA receptors. First, a new method to capture the structural features of DNA–drug complex architecture was proposed and then used to correlate the extracted features with binding affinity of the complexes

Distinguishing Single DNA Nucleotides Based on Their Times of Flight Through Nanoslits: A Molecular Dynamics Simulation Study

Brian R. Novak, Dorel Moldovan [North Carolina State University], Dimitris E. Nikitopoulos, and Steven A. Soper

J. Phys. Chem. B., **117**, 3271–3279, 2013**.**

A!

Transport of single molecules in nanochannels or nanoslits might be used to identify them via their transit (flight) times. In this paper, we present molecular dynamics simulations of transport of single deoxynucleotide 5′-monophoshates (dNMP) in aqueous solution under pressure-driven flow, to average velocities between 0.4 and 1.0 m/s, in 3 nm wide slits with hydrophobic walls. The simulation results show that, while moving along the slit, the mononucleotides are adsorbed and desorbed from the walls multiple times.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Does electron-correlation has any role in the quantitativestructure–activity relationships?

Vikas [Panjab University] ,Reenu, Chayawan

J. Mol.Graph. and Mod., **42,** 7–16, 2013.

For developing quantitative structure–activity relationships (QSARs), quantum-mechanical molecular descriptors based on the state-of-the-art quantum-mechanical methods such as Hartree–Fock (HF) method and density-functional theory (DFT), are now routinely employed. The validity of these quantum-mechanical methods, however, rests on the accurate estimation of electron-correlation energy. This work analyses the role of electron-correlation, using correlation energy as a molecular descriptor, in the QSARs.

Potentials and Parameters

Improved Generalized Born Solvent Model Parameters for Protein Simulations

Hai Nguyen, Daniel R. Roe, and Carlos Simmerling [Stony Brook University]

J. Chem. Theor. and Comp, **9**, 2020–2034, 2013.

The generalized Born (GB) model is one of the fastest implicit solvent models, and it has become widely adopted for Molecular Dynamics (MD) simulations. This speed comes with trade-offs, and many reports in the literature have pointed out weaknesses with GB models. Because the quality of a GB model is heavily affected by empirical parameters used in calculating solvation energy, in this work we have refit these parameters for GB-Neck, a recently developed GB model, in order to improve the accuracy of both the solvation energy and effective radii calculations.

Further insights in the ability of classical nonadditive potentials to model actinide ion–water interactions

Florent Réal [Université Lille 1 (Sciences et Technologies)], Michael Trumm, Bernd Schimmelpfennig, Michel Masella, Valérie Vallet

J. Comp. Chem., **34**, 707–719, 2013.

Pursuing our efforts on the development of accurate classical models to simulate radionuclides in complex environments (Réal et al., J. Phys. Chem. A 2010, 114, 15913; Trumm et al. J. Chem. Phys. 2012, 136, 044509), this article places a large emphasis on the discussion of the influence of models/parameters uncertainties on the computed structural, dynamical, and temporal properties. Two actinide test cases, trivalent curium and tetravalent thorium, have been studied with three different potential energy functions, which allow us to account for the polarization and charge-transfer effects occurring in hydrated actinide ion systems.

Solvation energy

Extended solvent-contact model for protein solvation: Test cases for dipeptides

Hwanho Choi, Hongsuk Kang, Hwangseo Park[Sejong University].

J. Mol.Graph. and Mod., **42,** 50–59, 2013.

Solvation effects are critically important in the structural stabilization and functional optimization of proteins. Here, we propose a new solvation free energy function for proteins, and test its applicability in predicting the solvation free energies of dipeptides. The present solvation model involves the improvement of the previous solvent-contact model assuming that the molecular solvation free energy could be given by the sum over the individual atomic contributions.

Solute and Solvent Dynamics in Confined Equal-Sized Aqueous Environments of Charged and Neutral Reverse Micelles: A Combined Dynamic Fluorescence and All-Atom Molecular Dynamics Simulation Study

Biswajit Guchhait and Ranjit Biswas , Pradip K. Ghorai [Indian Institute of Science Education and Research, Kolkata]

J. Phys. Chem. B., **117**, 3345–3361, 2013**.**

Here a combined dynamic fluorescence and all-atom molecular dynamics simulation study of aqueous pool-size dependent solvation energy and rotational relaxations of a neutral dipolar solute, C153, trapped in AOT (charged) and IGPAL (neutral) reverse micelles (RMs) at 298 K, is described. RMs in simulations have been represented by a reduced model where SPC/E water molecules interact with a trapped C153 that possesses realistic charge distributions for both ground and excited states. In large aqueous pools, measured average solvation and rotation rates are smaller for the neutral RMs than those in charged ones.

Molecular Dynamics

Molecular Modeling and Molecular Dynamics Simulations of Recombinase Rad51

Yuichi Kokabu, Mitsunori Ikeguchi[Yokohama City University]

Biophysical Journal. **104**, 1556-1565, 2013.

The Rad51 ATPase plays central roles in DNA homologous recombination. Yeast Rad51 dimer structure in the active form of the filament was constructed using homology modeling techniques, and all-atom molecular dynamics (MD) simulations were performed using the modeled structure. We found two crucial interaction networks involving ATP: one is among the γ-phosphate of ATP, K^+ ions, H352, and D374; the other is among the adenine ring of ATP, R228, and P379. Multiple MD simulations were performed in which the number of bound K^+ ions was changed.

A

Molecular Dynamics (Cont'd)

Advanced techniques for constrained internal coordinate molecular dynamics

Jeffrey R. Wagner, Gouthaman S. Balaraman, Michiel J. M. Niesen, Adrien B. Larsen, Abhinandan Jain, Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Comp. Chem., **34**, 904–914, 2013.

A!

Internal coordinate molecular dynamics (ICMD) methods provide a more natural description of a protein by using bond, angle, and torsional coordinates instead of a Cartesian coordinate representation. Freezing high-frequency bonds and angles in the ICMD model gives rise to constrained ICMD (CICMD) models. In this article, we have designed a new framework for (1) initializing velocities for nonindependent CICMD coordinates, (2) efficient computation of center of mass velocity during CICMD simulations, (3) using advanced integrators such as Runge–Kutta, Lobatto, and adaptive CVODE for CICMD simulations, and (4) cancelling out the "flying ice cube effect" that sometimes arises in Nosé–Hoover dynamics.

Zwitterion l-cysteine adsorbed on the Au_{20} cluster: enhancement of infrared active normal modes

Alfredo Tlahuice-Flores [University of Texas at San Antonio]

J. Mol.Mod., **19,** 1937-1942 , 2013.

The study reported herein addressed the structure, adsorption energy and normal modes of zwitterion l-cysteine (Z-cys) adsorbed on the Au_{20} cluster by using density functional theory (DFT). It was found that four Z-cys are bound to the Au_{20} apexes preferentially through S atoms. Regarding normal modes, after adsorption of four Z-cys molecules, a more intense infrared (IR) peak is maintained around 1,631.4 cm^{-1} corresponding with a C=O stretching mode, but its intensity is enhanced approximately six times. . The enhancement in the intensity of modes between 0 to 300 cm^{-1} is around 4.5 to 5.0 times for normal modes that involve O–C=O and C-S bending modes.

Reliable Oligonucleotide Conformational Ensemble Generation in Explicit Solvent for Force Field Assessment Using Reservoir Replica Exchange Molecular Dynamics Simulations

Niel M. Henriksen, Daniel R. Roe, and Thomas E. Cheatham, III [University of Utah]

J. Phys. Chem. B., 117**, 4014–4027, 2013**.

Molecular dynamics force field development and assessment requires a reliable means for obtaining a well-converged conformational ensemble of a molecule in both a time-efficient and cost-effective manner. This remains a challenge for RNA because its rugged energy landscape results in slow conformational sampling and accurate results typically require explicit solvent which increases computational cost. To address this, we performed both traditional and modified replica exchange molecular dynamics simulations on a test system (alanine dipeptide) and an RNA tetramer known to populate A-form-like conformations in solution (single-stranded rGACC).

Molecular Dynamics (Cont'd)

Study of the Structural Role of Gallium and Aluminum in 45S5 Bioactive Glasses by Molecular Dynamics Simulations

Gianluca Malavasi, Alfonso Pedone[University of Modena and Reggio Emilia], and Maria Cristina Menziani

J. Phys. Chem. B., **117**, 4142–4150, 2013**.**

The structural properties of phosphosilicate glasses based on the 45S5 Bioglass doped with gallium and aluminum ($46.2\ SiO_2 \cdot 24.3Na_2O \cdot 26.9CaO \cdot 2.6P_2O_5 \cdot 1.0X_2O_3$, X = Ga or Al) are investigated by means of classical molecular dynamics simulations. Structural features of the two compositions are compared with those of the original 45S5 Bioglass in order to relate them to the different known bioactivities of these materials. Differences in the coordination environments of Ga and Al, network connectivity, and ion aggregation reveal a microscopic model of these glasses which supports the interpretation of the experimental data and provides new insight into the different biological behaviors of Ga- and Al-containing phosphosilicate glasses

Monte Carlo

Mixed Monte Carlo/Molecular Dynamics simulations of the prion protein

Andre A.S.T. Ribeiro [Cidade Universitaria],Ricardo B. de Alencastro

J. Mol.Graph. and Mod., **42** 1–6, 2013.

In this paper we present the results of mixed Monte Carlo/Molecular Dynamics (MC/MD) simulations of the D178N mutant of the human prion protein. We have used the MC moves for polypeptide sampling known as Concerted Rotations with Angles (CRA) to selectively sample the region of the prion protein comprising the β-sheet and one of the α-helices. The results indicate that the MC/MD simulations sample the phase space substantially faster than regular Molecular Dynamics simulations starting with the same initial conditions.

Free Energy Perturbation

Molecular Mechanism of Polyacrylate Helix Sense Switching across Its Free Energy Landscape

Adriana Pietropaolo and Tamaki Nakano [Hokkaido University]

J. Am. Chem. Soc., 2013, **135** , 5509–5512

Helical polymers with switchable screw sense are versatile frameworks for chiral functional materials. In this work, we reconstructed the free energy landscape of helical poly(2,7-bis(4-*tert*-butylphenyl)fluoren-9-yl acrylate) [poly(BBPFA)], as its racemization is selectively driven by light without any rearrangement of chemical bonds. The chirality inversion was enforced by atomistic free energy simulations using chirality indices as reaction coordinates. The free energy landscape reproduced the experimental electronic circular dichroism spectra.

Free Energy Perturbation (Cont'd)

Free Energy Calculations with Reduced Potential Cutoff Radii

Stuart J. Davie, James C. Reid, and Debra J. Searles [The University of Queensland]

J. Chem. Theor. and Comp, **9**, 2083–2089, 2013.

The Jarzynski Equality, the Crooks Fluctuation Theorem, and the Maximum Likelihood Estimator use a nonequilibrium approach for the determination of free energy differences due to a change in the state of a system. Here, this approach is used in combination with a novel transformation algorithm to increase computational efficiency in simulations with interacting particles, without losing accuracy.

Assessing the quality of absolute hydration free energies among CHARMM-compatible ligand parameterization schemes

Jennifer L. Knight, Joseph D. Yesselman , Charles L. Brooks III [University Avenue]

J. Comp. Chem., **34**, 893–903, 2013

A!

Multipurpose atom-typer for CHARMM (MATCH), an atom-typng toolset for molecular mechanics force fields, was recently developed in our laboratory. Here, we assess the ability of MATCH-generated parameters and partial atomic charges to reproduce experimental absolute hydration free energies for a series of 457 small neutral molecules in GBMV2, Generalized Born with a smooth SWitching (GBSW), and fast analytical continuum treatment of solvation (FACTS) implicit solvent models. The quality of hydration free energies associated with small molecule parameters obtained from ParamChem, SwissParam, and Antechamber are compared.

QM and QM/MM

Automated Fragmentation QM/MM Calculation of Amide Proton Chemical Shifts in Proteins with Explicit Solvent Model

Tong Zhu, John Z. H. Zhang, and Xiao He[East China Normal University]

J. Chem. Theor. and Comp, **9**, 2104–2114, 2013.

We have performed a density functional theory (DFT) calculation of the amide proton NMR chemical shift in proteins using a recently developed automated fragmentation quantum mechanics/molecular mechanics (AF-QM/MM) approach. Systematic investigation was carried out to examine the influence of explicit solvent molecules, cooperative hydrogen bonding effects, density functionals, size of the basis sets, and the local geometry of proteins on calculated chemical shifts. Our result demonstrates that the predicted amide proton (^1H_N) NMR chemical shift in explicit solvent shows remarkable improvement over that calculated with the implicit solvation model.

Quantum Mechanics/Molecular Mechanics Modeling of Fatty Acid Amide Hydrolase Reactivation Distinguishes Substrate from Irreversible Covalent Inhibitors

Alessio Lodola, Luigi Capoferri, Silvia Rivara, Giorgio Tarzia, Daniele Piomelli, Adrian Mulholland, and Marco Mor [Università degli Studi di Parma]

J.Med.Chem., **56,** 2500–2512, 2013.

A!

Carbamate and urea derivatives are important classes of fatty acid amide hydrolase (FAAH) inhibitors that carbamoylate the active-site nucleophile Ser241. In the present work, the reactivation mechanism of carbamoylated FAAH is investigated by means of a quantum mechanics/molecular mechanics (QM/MM) approach. The potential energy surfaces for decarbamoylation of FAAH covalent adducts, derived from the *O*-aryl carbamate URB597 and from the *N*-piperazinylurea JNJ1661610, were calculated and compared to that for deacylation of FAAH acylated by the substrate oleamide

QM and QM/MM (Cont'd)

The MM2QM tool for combining docking, molecular dynamics, molecular mechanics, and quantum mechanics[†]

Marcin Nowosielski, Marcin Hoffmann, Aneta Kuron, Malgorzata Korycka-Machala ,Jaroslaw Dziadek

J. Comp. Chem., **34**, 750–756 , 2013.

The use of the MM2QM tool in a combined docking + molecular dynamics (MD) + molecular mechanics (MM) + quantum mechanical (QM) binding affinity prediction study is presented, and the tool itself is discussed. The system of interest is *Mycobacterium tuberculosis (MTB*) pantothenate synthetase in complexes with three highly similar sulfonamide inhibitors, for which crystal structures are available.

A!

Calculation of wave-functions with frozen orbitals in mixed quantum mechanics/molecular mechanics methods. II. Application of the local basis equation

György G. Ferenczy[Semmelweis University]

J. Comp. Chem., **34**, 862–869, 2013.

The application of the local basis equation (Ferenczy and Adams, *J. Chem. Phys*. **2009**, *130*, 134108) in mixed quantum mechanics/molecular mechanics (QM/MM) and quantum mechanics/quantum mechanics (QM/QM) methods is investigated. This equation is suitable to derive local basis nonorthogonal orbitals that minimize the energy of the system and it exhibits good convergence properties in a self-consistent field solution. These features make the equation appropriate to be used in mixed QM/MM and QM/QM methods to optimize orbitals in the field of frozen localized orbitals connecting the subsystems.

Caffeine as base analogue of adenine or guanine: A theoretical study

Ali Ebrahimi, Mostafa Habibi-Khorassani, Farideh Badichi Akher[University of Sistan & Baluchestan] , Abdolkarim Farrokhzadeh, Pouya Karimi

J. Mol.Graph. and Mod., **42,** 81–91, 2013.

The results of quantum mechanical calculations, including binding energies and results of the population analysis show that the GC and AT base pair complexes are more stable than the CAF-X ones (where CAF is caffeine and X = adenine (A), thymine (T), cytosine (C) and guanine (G)). Structural similarity between the CAF molecule and purine bases (G and A) provides the possibility of incorporation of the CAF molecule into the DNA macromolecule. By comparing the CAF-A and CAF-T complexes with the AT base pair, and the CAF-G and CAF-C complexes with the GC base pair, it was found that the formation of the CAF-T complex is more probable than the other complexes.

Microsolvation of Mg^{2+}, Ca^{2+}: strong influence of formal charges in hydrogen bond networks

Juan David Gonzalez, Elizabeth Florez, Jonathan Romero, Andrés Reyes, Albeiro Restrepo[Universidad de Antioqui]

J. Mol.Mod., **19,** 1763-1777, 2013.

A stochastic exploration of the quantum conformational spaces in the microsolvation of divalent cations with explicit consideration of up to six solvent molecules [$Mg(H_2O)_n)]^{2+}$, ($n = 3, 4, 5, 6$) at the B3LYP, MP2, CCSD(T) levels is presented. We find several cases in which the formal charge in Mg^{2+} causes dissociation of water molecules in the first solvation shell, leaving a hydroxide ion available to interact with the central cation, the released proton being transferred to outer solvation shells in a Grotthus type mechanism; this particular finding sheds light on the capacity of Mg^{2+} to promote formation of hydroxide anions, a process necessary to regulate proton transfer in enzymes with exonuclease activity.

QM and QM/MM (Cont'd)

Quantum chemical study of silanediols as metal binding groups for metalloprotease inhibitors

Igor S. Ignatyev, Manuel Montejo, Pilar Gema Rodríguez Ortega, Juan Jesús López González[St. Petersburg State University]

J. Mol.Mod., **19,** 1819-1834, 2013.

DFT (B3LYP and M06L) as well as *ab initio* (MP2) methods with Dunning cc-pVnZ (n = 2,3) basis sets are employed for the study of the binding ability of the new class of protease inhibitors, i.e., silanediols, in comparison to the well-known and well-studied class of inhibitors with hydroxamic functionality (HAM). Active sites of metalloproteases are modeled by $[R_3M\text{-}OH_2]^{2+}$ complexes, where R stands for ammonia or imidazole molecules and M is a divalent cation, namely zinc, iron or nickel (in their different spin states). The inhibiting activity is estimated by calculating Gibbs free energies of the water displacement by metal binding groups (MBGs) according to: $[R_3M\text{-}OH_2]^{2+}$ + MBG → $[R_3M\text{-}MBG]^{2+}$ + H_2O.

QM/MM Modeling of Environmental Effects on Electronic Transitions of the FMO Complex

Junkuo Gao, Wu-Jun Shi, Jun Ye, Xiaoqing Wang, Hajime Hirao, and Yang Zhao [Nanyang Technological University,]

J. Phys. Chem. B., **117**, 3488–3495, 2013**.**

A!

The Fenna–Matthews–Olson (FMO) light harvesting pigment–protein complex in green sulfur bacteria transfers the excitation energy from absorbed sunlight to the reaction center with almost 100% quantum efficiency. The protein-pigment coupling (part of the environmental effects) is believed to play an important role in determining excitation energy transfer pathways. To study the effect of environment on the electronic transitions in the FMO complex, especially by taking into account the newly discovered eighth extra pigment, we have employed hybrid quantum-mechanics/molecular-mechanics (QM/MM) methods in combination with molecular dynamics (MD) simulations.

Spectroscopic investigations and hydrogen bond interactions of 8-aza analogues of xanthine, theophylline and caffeine: a theoretical study

Mylsamy Karthika, Ramasamy Kanakaraju[NGM College], Lakshmipathi Senthilkumar

J. Mol.Mod., **19,** 1835-1851, 2013.

The structure, spectral properties and the hydrogen bond interactions of 8-aza analogues of xanthine, theophylline and caffeine have been studied by using quantum chemical methods. The time-dependent density functional theory (TD-DFT) and the singly excited configuration interaction (CIS) methods are employed to optimize the excited state geometries of isolated 8-azaxanthine, 8-azatheophylline tautomers and 8-azacaffeine in both the gas and solvent phases. The solvent phase calculations are performed using the polarizable continuum model (PCM).

Quantum Mechanical Study on the Mechanism of Peptide Release in the Ribosome

Carles Acosta-Silva, Joan Bertran [Universitat Autònoma de Barcelona], Vicenç Branchadell, and Antoni Oliva

J. Phys. Chem. B., **117**, 3503–3515, 2013**.**

A quantum mechanical study of different concerted mechanisms of peptide release in the ribosome has been carried out using the M06-2X density functional. Reoptimization with MP2 has also been carried out for the stationary points of some selected mechanisms. The uncatalyzed processes in solution have been treated with the SMD solvation model. We conclude that the 2′-OH plays an important catalytic role and that it takes place via a zwitterionic transition state, this TS being stabilized by the presence of oxyanion holes or by the solvent.

Comparative or Homology Modeling

Improvements in Markov State Model Construction Reveal Many Non-Native Interactions in the Folding of NTL9

Christian R. Schwantes and Vijay S. Pande [Stanford University]

J. Chem. Theor. and Comp, **9**, 2000–2009, 2013.

Markov State Models (MSMs) provide an automated framework to investigate the dynamical properties of high-dimensional molecular simulations. These models can provide a human-comprehensible picture of the underlying process and have been successfully used to study protein folding, protein aggregation, protein ligand binding, and other biophysical systems. In the following, we suggest an improved method, which utilizes second order Independent Component Analysis (also known as time-structure based Independent Component Analysis, or tICA), to construct the state-space.

Cluster-based molecular docking study for *in silico* identification of novel 6-fluoroquinolones as potential inhibitors against *mycobacterium tuberculosis*

Nikola Minovski [National Institute of Chemistry,], Andrej Perdih, Marjana Novic, Tom Solmajer

J. Comp. Chem., **34**, 790–801, 2013.

A classical protein sequence alignment and homology modeling strategy were used for building three *Mycobacterium tuberculosis*-DNA gyrase protein models using the available topoII-DNA-6FQ crystal structure complexes originating from different organisms. The recently determined *M. tuberculosis*-DNA gyrase apoprotein structures and topoII-DNA-6FQ complexes were used for defining the 6-fluoroquinolones (6-FQs) binding pockets. The quality of the generated models was initially validated by docking of the cocrystallized ligands into their binding site, and subsequently by quantitative evaluation of their discriminatory performances (identification of active/inactive 6-FQs) for a set of 145 6-FQs with known biological activity values.

Mixing MARTINI: Electrostatic Coupling in Hybrid Atomistic–Coarse-Grained Biomolecular Simulations

Tsjerk A. Wassenaar, Helgi I. Ingólfsson, Marten Prieß, Siewert J. Marrink, and Lars V. Schäfer
[University Frankfurt]

J. Phys. Chem. B., **117**, 3516–3530, 2013**.**

Hybrid molecular dynamics simulations of atomistic (AA) solutes embedded in coarse-grained (CG) environment can substantially reduce the computational cost with respect to fully atomistic simulations. However, interfacing both levels of resolution is a major challenge that includes a balanced description of the relevant interactions. This is especially the case for polar solvents such as water, which screen the electrostatic interactions and thus require explicit electrostatic coupling between AA and CG subsystems. Here, we present and critically test computationally efficient hybrid AA/CG models. We combined the Gromos atomistic force field with the MARTINI coarse-grained force field.

Ligand Docking

Theory and Simulations of Adhesion Receptor Dimerization on Membrane Surfaces

Yinghao Wu, Barry Honig[Columbia University], Avinoam Ben-Shaul

Biophysical Journal. **104**, 1221-1229, 2013.

The equilibrium constants of *trans* and *cis* dimerization of membrane bound (2D) and freely moving (3D) adhesion receptors are expressed and compared using elementary statistical-thermodynamics. Both processes are mediated by the binding of extracellular subdomains whose range of motion in the 2D environment is reduced upon dimerization, defining a thin reaction shell where dimer formation and dissociation take place. We show that the ratio between the 2D and 3D equilibrium constants can be expressed as a product of individual factors describing, respectively, the spatial ranges of motions of the adhesive domains, and their rotational freedom within the reaction shell.

Ligand-Optimized Homology Models of D_1 and D_2 Dopamine Receptors: Application for Virtual Screening

Marcin Kołaczkowski [Jagiellonian University Collegium Medicum], Adam Bucki, Marcin Feder, and Maciej Pawłowski

J.Chem. Infor. and Mod. **53**, 638–648, 2013.

S!

Recent breakthroughs in crystallographic studies of G protein-coupled receptors (GPCRs), together with continuous progress in molecular modeling methods, have opened new perspectives for structure-based drug discovery. A crucial enhancement in this area was development of induced fit docking procedures that allow optimization of binding pocket conformation guided by the features of its active ligands. In the course of our research program aimed at discovery of novel antipsychotic agents, our attention focused on dopaminergic D_2 and D_1 receptors (D_2R and D_1R).

Prediction of Ligand-Induced Structural Polymorphism of Receptor Interaction Sites Using Machine Learning

Daisuke Takaya, Tomohiro Sato, Hitomi Yuki, Shunta Sasaki, Akiko Tanaka, Shigeyuki Yokoyama, and Teruki Honma [RIKEN Systems and Structural Biology Center]

J.Chem. Infor. and Mod. **53**, 704–716, 2013.

Protein functions are closely related to their three-dimensional structures. Various degrees of conformational changes in the main and side chains occur when binding with other molecules, such as small ligands or proteins. The ligand-induced structural polymorphism of proteins is also referred to as “induced-fit”, and it plays an important role in the recognition of a particular class of ligands as well as in signal transduction. We have developed new prediction models that discriminate conformationally fluctuant residues caused by ligand-binding. The training and test data sets were obtained from the Protein Data Bank. The induced-fit residues were judged based on the Z values of the Cα atom distances in each protein cluster

Ligand Docking (Cont'd)

Determination of key receptor–ligand interactions of dopaminergic arylpiperazines and the dopamine D2 receptor homology model

Vladimir Sukalovic[University of Belgrade], Vukic Soskic, Milan Sencanski, Deana Andric, Sladjana Kostic-Rajacic

J. Mol.Mod., **19,** 1751-1762 , 2013.

Interest in structure-based G-protein-coupled receptor (GPCR) ligand discovery is huge, given that almost 30 % of all approved drugs belong to this category of active compounds. The GPCR family includes the dopamine receptor subtype D2 (D2DR), but unfortunately—as is true of most GPCRs—no experimental structures are available for these receptors. In this publication, we present the molecular model of D2DR based on the previously published crystal structure of the dopamine D3 receptor (D3DR).

A!

Structural analysis of Pla protein from the biological warfare agent Yersinia pestis: docking and molecular dynamics of interactions with the mammalian plasminogen system

Eduardo Ruback, Leandro Araujo Lobo, Tanos Celmar Costa França & Pedro Geraldo Pascutti [Federal University of Rio de Janeiro]

J. Biomol. Stru. and Dyn., **31**, 477-484, 2013.

Yersinia pestis protein Pla is a plasmid-coded outer membrane protein with aspartic-protease activity. Pla exhibits a plasminogen (Plg) activator activity (PAA) that promotes the cleavage of Plg to the active serine-protease form called plasmin. Exactly how Pla activates Plg into plasmin remains unclear. To investigate this event, we performed the interactions between the predicted Plg and Pla protein structures by rigid-body docking with the HEX program and evaluated the complex stability by molecular dynamics (MD) using the GROMACS package programs.

Molecular simulations study of ligand-release mechanism in an odorant-binding protein from the southern house mosquito

Hui Yu, Xi Zhao, Xian-li Feng, Xuecheng Chen, Ewa Borowiak-Palen & Xu-ri Huang **[**Jilin University]

J. Biomol. Stru. and Dyn., **31**, 485-494, 2013.

Pheromone-binding proteins transport hydrophobic pheromones through the aqueous medium to their receptors. The odorant-binding protein (OBP) of *Culex quinquefasciatus* (CquiOBP1), which binds to an oviposition pheromone (5R,6S)-6-acetoxy-5-hexadecanolide (MOP), plays a key role in sensing oviposition cues. However, so far the mechanism of MOP release from the protein is unclear. Therefore, in this contribution the process and pathway of the MOP release from CquiOBP1 are determined by conventional molecular dynamics, essential dynamics (ED), and ED sampling.

Molecular Determinants of Binding to the *Plasmodium* Subtilisin-like Protease 1

Simone Fulle [Oxford Centre for Innovation], Chrislaine Withers-Martinez, Michael J. Blackman, Garrett M. Morris, and Paul W. Finn

J.Chem. Infor. and Mod. **53**, 573–583, 2013.

PfSUB1, a subtilisin-like protease of the human malaria parasite *Plasmodium falciparum,* is known to play important roles during the life cycle of the parasite and has emerged as a promising antimalarial drug target. In order to provide a detailed understanding of the origin of binding determinants of PfSUB1 substrates, we performed molecular dynamics simulations in combination with MM-GBSA free energy calculations using a homology model of PfSUB1 in complex with different substrate peptides.

Ligand Docking (Cont'd)

The Impact of Introducing a Histidine into an Apolar Cavity Site on Docking and Ligand Recognition

Matthew Merski and Brian K. Shoichet [University of California San Francisco]

J.Med.Chem., **56,** 2874–2884, 2013.

Simplified model binding sites allow one to isolate entangled terms in molecular energy functions. Here, we investigate the effects on ligand recognition of the introduction of a histidine into a hydrophobic cavity in lysozyme. We docked 656040 molecules and tested 26 highly and nine poorly ranked. Twenty-one highly ranked molecules bound and five were false positives, while three poorly ranked molecules were false negatives. In the 16 X-ray complexes now known, the docking predictions overlaid well with the crystallographic results

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3. JOURNAL REVIEWS

Journal of Computatianl Chemistry, 34 (9,10, 11), April, 2013.

707–719 **Further insights in the ability of classical nonadditive potentials to model actinide ion–water interactions** Florent Réal [Université Lille 1 (Sciences et Technologies)]Michael Trumm, Bernd Schimmelpfennig, Michel Masella, Valérie Vallet

See Methodology / Potentials and Parameters

720–730 **Efficient implementation of restricted active space configuration interaction with the hole and particle approximation** David Casanova [Universitat de Barcelona]

The restricted active space configuration interaction (RASCI) formalism with the hole and particle truncation of the wavefunction, that is, RASCI(h,p), holds very nice properties such as balanced treatment of ground and low-lying excited states, spin-completeness, large flexibility of the wavefunction, and moderate computational cost. In this article, I present a new implementation of the RASCI(h,p) method using a general algorithm based on the integral-driven approach.

731–738 **Membrane protein native state discrimination by implicit membrane models** Olga Yuzlenko, Themis Lazaridis [City College of the City University of New York]

See Applications / Membrane Proteins and Lipid-Peptide Interactions

739–749 **A valence bond model for aqueous Cu(II) and Zn(II) ions in the AMOEBA polarizable force field** Jin Yu Xiang, Jay W. Ponder [Washington University in St. Louis]

A general molecular mechanics (MM) model for treating aqueous Cu^{2+} and Zn^{2+} ions was developed based on valence bond (VB) theory and incorporated into the atomic multipole optimized energetics for biomolecular applications (AMOEBA) polarizable force field.

750–756 **The MM2QM tool for combining docking, molecular dynamics, molecular mechanics, and quantum mechanics**[†] Marcin Nowosielski, Marcin Hoffmann, Aneta Kuron, Malgorzata Korycka-Machala ,Jaroslaw Dziadek

See Applications / QM/MM.

827–835 **Spectroscopic fingerprints of toroidal nuclear quantum delocalization via *Ab Initio* path integral simulations** Ole Schütt, Daniel Sebastiani[Martin-Luther University Halle-Wittenberg,]

We investigate the quantum-mechanical delocalization of hydrogen in rotational symmetric molecular systems.

836–846 **Simulating GTP:Mg and GDP:Mg with a simple force field: A structural and thermodynamic analysis** Thomas Simonson [Laboratoire de Biochimie], Priyadarshi Satpati

Di- and tri-phosphate nucleotides are essential cofactors for many proteins, usually in an Mg^{2+}-bound form. Proteins like GTPases often detect the difference between NDP and NTP and respond by changing conformations. To study such complexes, simple, fixed charge force fields have been used, which allow long simulations and precise free energy calculations.

847–853 **A numerically stable restrained electrostatic potential charge fitting method** Juan Zeng, LiLi Duan, John Z.H. Zhang, Ye Mei [East China Normal University]

Inspired by the idea of charge decomposition in calculation of the dipole preserving and polarization consistent charges (Zhang et al., J. Comput. Chem. 2011, 32, 2127), we have proposed a numerically stable restrained electrostatic potential (ESP)-based charge fitting method for protein.

854–861 **Calculation of wave-functions with frozen orbitals in mixed quantum mechanics/molecular mechanics methods. Part I. Application of the Huzinaga equation** György G. Ferenczy [Semmelweis University Budapest,]

Mixed quantum mechanics/quantum mechanics (QM/QM) and quantum mechanics/molecular mechanics (QM/MM) methods make computations feasible for extended chemical systems by separating them into subsystems that are treated at different level of sophistication. . The theoretical background and the practical aspects of the application of the Huzinaga equation in mixed methods are discussed.

862–869 **Calculation of wave-functions with frozen orbitals in mixed quantum mechanics/molecular mechanics methods. II. Application of the local basis equation** György G. Ferenczy[Semmelweis University]

See Applications / QM/MM.

870–878 **Assessment of density functional methods for reaction energetics: Iridium-catalyzed water oxidation as case study** Andranik Kazaryan, Evert Jan Baerends[VU University Amsterdam]

We investigate basis set convergence for a series of density functional theory (DFT) functionals (both hybrid and nonhybrid) and compare to coupled-cluster with single and double excitations and perturbative triples [CCSD(T)] benchmark calculations.

879–891 **Structure-based redesign of proteins for minimal T-cell epitope content** Yoonjoo Choi, Karl E. Griswold, Chris Bailey-Kellogg [Dartmouth College]

See Applications / Protein Structure Analysis.

893–903 **Assessing the quality of absolute hydration free energies among CHARMM-compatible ligand parameterization schemes** Jennifer L. Knight, Joseph D. Yesselman , Charles L. Brooks III [University Avenue]

See Methodology /Free Energy Perturbation

904–914 **Advanced techniques for constrained internal coordinate molecular dynamics** Jeffrey R. Wagner, Gouthaman S. Balaraman, Michiel J. M. Niesen, Adrien B. Larsen, Abhinandan Jain, Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

See Methodology / Molecular Dynamics.

915–927 **Message passing interface and multithreading hybrid for parallel molecular docking of large databases on petascale high performance computing machines** Xiaohua Zhang, Sergio E. Wong, Felice C. Lightstone[Lawrence Livermore National Lab]

See Applications / Bioinformatics.

928–937 **Adjustment of born-oppenheimer electronic wave functions to simplify close coupling calculations**Robert J. Buenker [Universität Wuppertal] , Heinz-Peter Liebermann[1], Yu Zhang[2,3], Yong Wu[3,4], Lingling Yan[2], Chunhua Liu[2,3], Yizhi Qu[2], Jianguo Wang

Technical problems connected with use of the Born-Oppenheimer clamped-nuclei approximation to generate electronic wave functions, potential energy surfaces (PES), and associated properties are discussed.

938–951 **Quantum monte carlo for large chemical systems: Implementing efficient strategies for petascale platforms and beyond** Anthony Scemama, Michel Caffarel, Emmanuel Oseret, William Jalby

Various strategies to implement efficiently quantum Monte Carlo (QMC) simulations for large chemical systems are presented. These include: (i) the introduction of an efficient algorithm to calculate the computationally expensive Slater matrices.

952–957 **After the electronic field: Structure, bonding, and the first hyperpolarizability of HArF** Heng-Qing Wu, Rong-Lin Zhong, Yu-He Kan, Shi-Ling Sun, Min Zhang, Hong-Liang Xu [Northeast Normal University,], Zhong-Min Su

In this work, we add different strength of external electric field (E_{ext}) along molecule axis (Z-axis) to investigate the electric field induced effect on HArF structure. The H-Ar bond is the shortest at $E_{ext} = -189 \times 10^{-4}$ and the Ar-F bond show shortest value at $E_{ext} = 185 \times 10^{-4}$ au.

958–964 **Long-range corrected functionals satisfy Koopmans' theorem: Calculation of correlation and relaxation energies** Rahul Kar, Jong-Won Song, Kimihiko Hirao[RIKEN Advanced Institute for Computational Science]

In this article, we show that the long-range-corrected (LC) density functionals LC-BOP and LCgau-BOP reproduce frontier orbital energies and highest-occupied molecular orbital (HOMO)—lowest-unoccupied molecular orbital (LUMO) gaps better than other density functionals.

965–973 **FEW: A workflow tool for free energy calculations of ligand binding** Nadine Homeyer, Holger Gohlke[Heinrich-Heine-University]

See Applications / Ligand Binding.

974–985 **TargetATPsite: A template-free method for ATP-binding sites prediction with residue evolution image sparse representation and classifier ensemble** Dong-Jun Yu, Jun Hu, Yan Huang,Hong-Bin Shen [Shanghai Jiao Tong University], Yong Qi[1,2], Zhen-Min Tang[1], Jing-Yu Yang[1]

See Applications / Protein-ligand.

Journal of Molecular Modeling, 19 (4), April, 2013.

1459-1471 **Microsolvation and hydration enthalpies of CaC2O4(H2O) n (n = 0-16) and C2O4 2-(H2O) n (n = 0-14): an ab initio study,** Victor M. Rosas-García, Isabel del Carmen Sáenz-Tavera, Verónica Janeth Rodríguez-Herrera, Benjamín Raymundo Garza-Campos[Universidad Autónoma de Nuevo León (UANL)]

We studied hydrated calcium oxalate and its ions at the restricted Hartree–Fock RHF/6-31G* level of theory. Performing a configurational search seems to improve the fit of the HF/6-31G* level to experimental data.

1473-1488 **Electronic structure and stabilities of Ni-doped germanium nanoclusters: a density functional modeling study,** Kapil Dhaka, Ravi Trivedi, Debashis Bandyopadhyay [Birla Institute of Technology and Science]

The present study reports the geometry, electronic structure, growth behavior and stability of neutral and ionized nickel encapsulated germanium clusters containing 1–20 germanium atoms within the framework of a linear combination of atomic orbital density functional theory (DFT) under a spin polarized generalized gradient approximation.

1565-1572 **Mechanistic investigations of $Al(OH)_3$ oligomerization mechanisms,** Xueli Cheng, Wenchao Ding, Yongjun Liu[Taishan University], Dairong Chen

Aluminum aerogels have extremely low thermal conductivities, and are ideal candidates for use in thermal superinsulators, adsorbents, sensors, catalyst carriers, and inorganic fillers. In the present work, the oligomerization mechanisms of $Al(OH)_3$ were investigated systematically with the Gaussian 03 package at the B3LYP/6-311++G(d,p) level in combination with CPCM single-point energy calculations.

1573-1582 **Structural and energetic insights into sequence-specific interaction in DNA–drug recognition: development of affinity predictor and analysis of binding selectivity,** Jingheng Ning[Jiangsu University], Weiwei Chen, Jiaojiao Li, Zaixi Peng, Jianhui Wang, Zhong Ni

See Applications / Protein-Nucleic acids.

1583-1590 **Theoretical studies on densities, stability and detonation properties of 2D polymeric complexes $Cu(DAT)_2Cl_2$ and its new analogues $Zn(DAT)_2Cl_2$,** Yuanjie Shu[Institute of Chemical Materials china], Huarong Li, Shijie Gao, Ying Xiong

A novel environmentally friendly octahedrally coordinated 2D polymeric complexes bis(1,5-diaminotetrazole) -dichlorozinc(II) ($Zn(DAT)_2Cl_2$) was first designed based on the the crystal data of bis(1,5-diaminotetrazole)-dichlorocopper(II) ($Cu(DAT)_2Cl_2$).

1591-1596 **Dynamic motion of La atom inside the C_{74} (D_{3h}) cage: a relativistic DFT study,** Dongxu Tian, Suzhen Ren, Ce Hao [Dalian University of Technology]

The interaction between lanthanum atom (La) and C_{74} (D_{3h}) was investigated by all-electron relativistic density function theory (DFT). With the aid of the representative patch of C_{74} (D_{3h}), we studied the interaction between C_{74} (D_{3h}) and La and obtained the interaction potential.

1597-1604 **Cyano or o-nitrophenyl? Which is the optimal electron-withdrawing group for the acrylic acid acceptor of D-π-A sensitizers in DSSCs? A density functional evaluation,** Ji Zhang, Yu-He Kan,Hai-Bin Li,Yun Geng,Yong Wu,Yu-Ai Duan, Zhong-Min Su[Northeast Normal University]

We report a DFT, TDDFT and DFTB investigation of the performance of two donor-π-acceptor (D-π-A)-type organic dyes bearing different electron-withdrawing groups (EWG) for dye-sensitized solar cells (DSSCs) to evaluate which EWG is better for an acrylic acid acceptor, i.e., Cyano (–CN) or *o*-nitrophenyl (*o*-NO_2–Ph).

1605-1615 **Study of DNA base-Li doped SiC nanotubes in aqueous solutions: a computer simulation study,** Sepideh Ketabi[Islamic Azad University], Seyed Majid Hashemianzadeh, Morteza MoghimiWaskasi

See Applications / Protein-Nucleic acids.

1617-1626 **Theoretical studies on the unimolecular decomposition of nitroglycerin,** Qingli Yan, Weihua Zhu, Aimin Pang, Xuhui Chi, Xijuan Du, Heming Xiao [Nanjing University of Science and Technology]

To improve the understanding of the unimolecular decomposition mechanism of nitroglycerin (NG) in the gas phase, density functional theory calculations were performed to determine various decomposition channels at the B3LYP/6-311G** level.

1627-1639 **Study of the aggregation mechanism of polyglutamine peptides using replica exchange molecular dynamics simulations,** Miki Nakano, Kuniyoshi Ebina, Shigenori Tanaka [Kobe University]

See Applications / Protein Dynamics.

1641-1650 **Interactions of hydrogen molecules with complexes of lithium cation and aromatic nitrogen-containing heterocyclic anions,** Yingxin Sun, Huai Sun[Shanghai Jiao Tong University]

Highly stable salt functional groups consisting of lithium cation and aromatic anions ($C_nH_nN_{5-n}$−Li) are studied for hydrogen storage using ab initio calculations, force field development, and grand canonical Monte Carlo simulations.

1651-1666 **Targeted molecular dynamics (TMD) of the full-length KcsA potassium channel: on the role of the cytoplasmic domain in the opening process,** Yan Li, Florent Barbault, Michel Delamar[Univ Paris Diderot, Sorbonne Paris Cité], Ruisheng Zhang, Rongjing Hu

See Applications / Protein Dynamics.

1667-1675 **Silicon–doping in carbon nanotubes: formation energies, electronic structures, and chemical reactivity,** Ruixin Bian, Jingxiang Zhao, Honggang Fu [Heilongjiang University]

See Applications / Carbon Nanotubes.

1677-1683 **Shape entropy's response to molecular ionization,** K. Pineda-Urbina, R. D. Guerrero, A. Reyes, Z. Gómez-Sandoval, R. Flores-Moreno [Universidad de Guadalajara]

In this work we define a shape entropy by calculating the Shannon's entropy of the shape function. This shape entropy and its linear response to the change in the total number of electrons of the molecule are explored as descriptors of bonding properties.

1685-1693 **Theoretical investigation into optical and electronic properties of 1,8-naphthalimide derivatives,** Ruifa Jin[Chifeng University], Shanshan Tang

A series of 1,8-naphthalimide derivatives has been designed to explore their optical, electronic, and charge transport properties as charge transport and/or luminescent materials for organic light-emitting diodes (OLEDs).

1695-1704 **DFT studies on the intrinsic conformational properties of non-ionic pyrrolysine in gas phase,** Gunajyoti Das[North Eastern Hill University], Shilpi Mandal

B3LYP/6-31G(d,p) level of theory is used to carry out a detailed gas phase conformational analysis of non-ionized (neutral) pyrrolysine molecule about its nine internal back-bone torsional angles.

1929-1936 **First-principles vdW-DF investigation on the interaction between the oxazepam molecule and C_{60} fullerene,** Masoud Darvish Ganji [Islamic Azad University], Mahnaz Nashtahosseini, Saeed Yeganegi, Mahyar Rezvani

The interaction between oxazepam and C_{60} fullerene was explored using first-principles vdW-DF calculations. It was found that oxazepam binds weakly to the fullerene cage via its carbonyl group. The binding of oxazepam to C_{60} is affected drastically by nonlocal dispersion interactions, while vdW forces affect the corresponding geometries only a little.

1937-1942 **Zwitterion l-cysteine adsorbed on the Au_{20} cluster: enhancement of infrared active normal modes,** Alfredo Tlahuice-Flores [University of Texas at San Antonio]

See Methodology / Molecular Dynamics.

Journal of Molecular Graphics and Modeling, 42, April, 2013.

1–6 **Mixed Monte Carlo/Molecular Dynamics simulations of the prion protein,** Andre A.S.T. Ribeiro [Cidade Universitaria],Ricardo B. de Alencastro

See Methodology / Monte Carlo.

7–16 **Does electron-correlation has any role in the quantitative structure–activity relationships?,** Vikas [Panjab University] ,Reenu, Chayawan

See Methodology / QSAR.

7–25 **Pharmacophore modeling, virtual screening, docking and *in silico*ADMET analysis of protein kinase B (PKB β) inhibitors,** Vivek K[Nirma University, Ahmedabad]. Vyas ,Manjunath Ghate, Ashutosh Goel

See Applications / Medicinal Chemmistry and Drug Design.

26–31 **Theoretical study on the degradation of ADP-ribose polymer catalyzed by poly(ADP-ribose) glycohydrolase,** Qianqian Hou[a], Xin Hu[b], Xiang Sheng[a] ,Yongjun Liu [Shandong University], ,Chengbu Liu[a]

See Applications / Enzyme Catalysis.

32–38 **Rarefied gas flow through nanoscale tungsten channels,** M.S. Ozhgibesov[National Cheng Kung University] ,T.S. Leu, C.H. Cheng

The aim of this work is to investigate argon flow behaviors through the channels with three types of boundary conditions. Current work deals with numerical simulations of rarefied gas flow through nano-channels using the Molecular Dynamics method.

39–49 **Pharmacophore modeling, homology modeling, and *in silico*screening reveal mammalian target of rapamycin inhibitory activities for sotalol, glyburide, metipranolol, sulfamethizole, glipizide, and pioglitazone,** Mohammad A. Khanfar[a], Majed M. AbuKhader[b], Saja Alqtaishat[a], Mutasem O. Taha[University of Jordan]

See Applications / Medicinal Chemmistry and Drug Design.

50–59 **Extended solvent-contact model for protein solvation: Test cases for dipeptides,** Hwanho Choi, Hongsuk Kang, Hwangseo Park[Sejong University,]

See Methodology / Solvation Energy.

60–72 **A3 adenosine receptor: Homology modeling and 3D-QSAR studies,** Anna Maria Almerico [Università degli Studi di Palermo],Marco Tutone, Licia Pantano, Antonino Lauria

See Applications / Medicinal Chemmistry and Drug Design.

73–80 **Modeling of the energies and splitting of the *Qx* and *Qy* bands in positional isomers of zinc pyridinoporphyrazines by TDDFT approach: Can TDDFT help distinguishing the structural isomers?,** Yunling Gao, Victor N. Nemykin[University of Minnesota-Duluth]

Electronic structures, energies and splitting of the *Qx* and *Qy* bands for positional isomers of zinc mono-, di-, tri-, and tetra pyridinoporphyrazines as well as parent zinc phthalocyanine were investigated using density functional theory (DFT) and time-dependent (TD) DFT approaches.

81–91 **Caffeine as base analogue of adenine or guanine: A theoretical study,** Ali Ebrahimi, Mostafa Habibi-Khorassani, Farideh Badichi Akher[University of Sistan & Baluchestan] , Abdolkarim Farrokhzadeh, Pouya Karimi

See Methodology / QM and QM/MM.

92–103 **An *in silico* method for designing thermostable variant of a dimeric mesophilic protein based on its 3D structure,** Sohini Basu, Srikanta Sen[Molecular Modeling Group, Biolab, Chembiotek, TCG Lifesciences]

See Applications / Bioinformatics.

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1. APPLICATIONS

1.1. *Small Molecules*

Water and Solvation

Investigation of Ethanol–Peptide and Water–Peptide Interactions through Intermolecular Nuclear Overhauser Effects and Molecular Dynamics Simulations

J. T. Gerig[University of California]

J. Phys. Chem. B., **117**, 4880-4892, 2013**.**

Molecular dynamics simulations have been used to explore solvent–solute intermolecular nuclear Overhauser effects (NOEs) on NMR (nuclear magnetic resonance) signals of [val5]angiotensin dissolved in 35% ethanol–water (v/v). Consideration of chemical shift, coupling constant and intramolecular NOE data suggest that conformations of the peptide are adequately sampled by simulations of up to 0.6 μs duration. Calculated cross relaxation terms at 0 and 25 °C are compared to experimental values and to terms predicted using a particulate model of the solvent.

Medicinal Chemistry and Drug Design

Microwave assisted synthesis, cholinesterase enzymes inhibitory activities and molecular docking studies of new pyridopyrimidine derivatives

Alireza Basiri, Vikneswaran Murugaiyah [Universiti Sains Malaysia] , Hasnah Osman, Raju Suresh KumarYalda Kia, Mohamed Ashraf Ali

Bioorg. and Med.Chem., **21**, 3022–3031, 2013.

A series of hitherto unreported pyrido-pyrimidine-2-ones/pyrimidine-2-thiones were synthesized under microwave assisted solvent free reaction conditions in excellent yields and evaluated in vitro for their acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes inhibitory activity. Among the pyridopyrimidine derivatives, 7e and 7l displayed 2.5- and 1.5-fold higher enzyme inhibitory activities against AChE as compared to standard drug, galanthamine, with IC50 of 0.80 and 1.37 μM, respectively.

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Medicinal Chemistry and Drug Design (Cont'd)

Design, synthesis and pharmacological characterization of analogs of 2-aminoethyl diphenylborinate (2-APB), a known store-operated calcium channel blocker, for inhibition of TRPV6-mediated calcium transport

Alexandre Hofera, Gergely Kovacsb, Anna Zappatinia, Michele Leuenbergera, Matthias A. Hedigerb, Martin Lochnera [University of Bern] ,

Bioorg. and Med.Chem., **21**, 3202–3213, 2013.

2-Aminoethyl diphenylborinate (2-APB) is a known modulator of the IP3 receptor, the calcium ATPase SERCA, the calcium release-activated calcium channel Orai and TRP channels. More recently, it was shown that 2-APB is an efficient inhibitor of the epithelial calcium channel TRPV6 which is overexpressed in prostate cancer. We have conducted a structure–activity relationship study of 2-APB congeners to understand their inhibitory mode of action on TRPV6. Our data show that the diaryl borinate moiety is required for biological activity and that the substitution pattern of the aryl rings can influence TRPV6 versus SOCE inhibition.

Grid-based molecular footprint comparison method for docking and *de novo* design: Application to HIVgp41

Trent E. Balius, William J. Allen,Sudipto Mukherjee, Robert C. Rizzo

J. Comp. Chem., **34**, 1226–1240, 2013.

Scoring functions are a critically important component of computer-aided screening methods for the identification of lead compounds during early stages of drug discovery. Here, we present a new multigrid implementation of the footprint similarity (FPS) scoring function that was recently developed in our laboratory which has proven useful for identification of compounds which bind to a protein on a per-residue basis in a way that resembles a known reference.

Discovery of Highly Potent Microsomal Prostaglandin E2 Synthase 1 Inhibitors Using the Active Conformation Structural Model and Virtual Screen

Shan He , Cong Li , Ying Liu , and Luhua Lai [Peking University]

J.Med.Chem., **56,** 3296–3309, 2013.

Microsomal prostaglandin E2 synthase 1 (mPGES-1) has been identified as a promising drug target due to its key role in prostaglandin biosynthesis. However, the lack of a well-characterized structure constitutes a great challenge for the development of inhibitors. Recently, we have built a model for the active conformation of mPGES-1. In the present study, the model was used for structure-based virtual screen of novel mPGES-1 inhibitors. Of the 142 compounds tested in the cell-free assay, 10 molecules are highly potent with IC50values of single digit nanomolar and the strongest inhibition of 1.1 nM.

Structural, Kinetic, and Pharmacodynamic Mechanisms of d-Amino Acid Oxidase Inhibition by Small Molecules

Seth C. Hopkins [Sunovion Pharmaceuticals Inc., Marlborough,], Michele L. R. Heffernan, Lakshmi D. Saraswat, Carrie A. Bowen, Laurence Melnick, Larry W. Hardy, Michael A. Orsini, Michael S. Allen, Patrick Koch, Kerry L. Spear, Robert J. Foglesong, Mustapha Soukri, Milan Chytil, Q. Kevin Fang, Steven W. Jones, Mark A. Varney, Aude Panatier, Stephane H. R. Oliet, Loredano Pollegioni, Luciano Piubelli, Gianluca Molla, Marco Nardini, and Thomas H. Large

J.Med.Chem., **56,** 3710–3724, 2013.

We characterized the mechanism and pharmacodynamics of five structurally distinct inhibitors of D-amino acid oxidase. All inhibitors bound the oxidized form of human enzyme with affinity slightly higher than that of benzoate (Kd ≈ 2–4 μM). Stopped-flow experiments showed that pyrrole-based inhibitors possessed high affinity (Kd ≈ 100–200 nM) and slow release kinetics ($k < 0.01$ s^{-1}) in the presence of substrate, while inhibitors with pendent aromatic groups altered conformations of the active site lid, as evidenced by X-ray crystallography, and showed slower kinetics of association.

Medicinal Chemistry and Drug Design (Cont'd)

Pyridine-Substituted Desoxyritonavir Is a More Potent Inhibitor of Cytochrome P450 3A4 than Ritonavir

Irina F. Sevrioukova[University of California] and Thomas L. Poulos

J.Med.Chem., **56,** 3733–3741, 2013.

Utilization of the cytochrome P450 3A4 (CYP3A4) inhibitor ritonavir as a pharmacoenhancer for anti-HIV drugs revolutionized the treatment of HIV infection. However, owing to ritonavir-related complications, there is a need for development of new CYP3A4 inhibitors with improved pharmacochemical properties, which requires a full understanding of the CYP3A4 inactivation mechanisms and the unraveling of possible inhibitor binding modes. We investigated the mechanism of CYP3A4 interaction with three desoxyritonavir analogues, containing the heme-ligating imidazole, oxazole, or pyridine group instead of the thiazole moiety.

3D shape-based analysis of cell line-specific compound response in cancers

Ningning He, Xiaoqi Wang, Nayoung Kim, Jong-Seok Lim, Sukjoon Yoon[Sookmyung Women's University],

J. Mol.Graph. and Mod., **42** 41–46, 2013.

The rapid increase in the volume of high-throughput anticancer chemical screening data requires a better interpretation of the relationships between diverse chemical structures and their varied effects in distinct cancer subtypes. Unexpected compound efficacy or resistance in cancer cells has been difficult to explain, in part because there has been no systematic analysis of compound response profiles in cancer cells with different genotypic backgrounds. The present analyses provide useful guidelines for investigating the lineage- and genotype-specific activities of diverse compounds and their mechanisms of action.

An Extensive and Diverse Set of Molecular Overlays for the Validation of Pharmacophore Programs

Ilenia Giangreco[AstraZeneca, Mereside, Alderley Park], David A. Cosgrove , and Martin J. Packer

J.Chem. Infor. and Mod. **53**, 852–866, 2013.

The pharmacophore hypothesis plays a central role in both the design and optimization of drug-like ligands. Pharmacophore patterns are invoked to explain the binding affinity of ligands and to enable the design of chemically distinct scaffolds that show affinity for a protein target. The importance of pharmacophores in rationalizing ligand affinity has led to numerous algorithms that seek to overlay ligands based on their pharmacophoric features. All such algorithms must be validated with respect to known ligand overlays, usually by extracting ligand overlay sets from the PDB.

Pharmacophore and 3D-QSAR Characterization of 6-Arylquinazolin-4-amines as Cdc2-like Kinase 4 (Clk4) and Dual Specificity Tyrosine-phosphorylation-regulated Kinase 1A (Dyrk1A) Inhibitors

Yongmei Pan, Yanli Wang, and Stephen H. Bryant [National Institution of Health, Bethesda]

J.Chem. Infor. and Mod. **53**, 938–947, 2013.

S!

Cdc2-like kinase 4 (Clk4) and dual specificity tyrosine-phosphorylation-regulated kinase 1A (Dyrk1A) are protein kinases that are promising targets for treatment of diseases caused by abnormal gene splicing. 6-Arylquinazolin-4-amines have been recently identified as potent Clk4 and Dyrk1A inhibitors. In order to understand the structure–activity correlation of these analogs, we have applied ligand-based pharmacophore and 3D-QSAR modeling combined with structure-based homology modeling and docking. The high R2 and Q2 based on validation with training and test set compounds suggested that the generated 3D-QSAR models are reliable in predicting novel ligand activities against Clk4 and Dyrk1A.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of Novel Phosphodiesterase-4D Inhibitors Prescreened by Molecular Dynamics-Augmented Modeling and Validated by Bioassay

Zhe Li, Ying-Hong Cai, Yuen-Kit Cheng, Xiao Lu, Yong-Xian Shao, Xingshu Li, Ming Liu, Peiqing Liu, and Hai-Bin Luo [Sun Yat-Sen University]

J.Chem. Infor. and Mod. **53**, 972–981, 2013.

Phosphodiesterase-4D (PDE4D) has been proved to be a potential therapeutic target against strokes. In the present study, a procedure of integrating pharmacophore, molecular docking, MD simulations, binding free energy calculations, and finally validation with bioassay was developed and described to search for novel PDE4D inhibitors from the SPECS database. Among the 29 compounds selected by our MD-augmented strategy, 15 hits were found with IC50 between 1.9 and 50 μM (a hit rate of 52%) and 6 potent hits showed IC50 less than 10 μM, which suggested that MD simulations can explore the intermolecular interactions of PDE4D–inhibitor complexes more precisely and thus significantly enhanced the hit rate of this screening.

Host-Guest Systems

Enthalpic Signature of Methonium Desolvation Revealed in a Synthetic Host–Guest System Based on Cucurbit[7]uril

Yi Wang, Jason R. King, Pan Wu, Daniel L. Pelzman, David N. Beratan [Duke University Medical Center], and Eric J. Toone

J. Am. Chem. Soc., 2013, **135**, 6084–6091

A!

Methonium (N+Me3) is an organic cation widely distributed in biological systems. The appearance of methonium in biological transmitters and receptors seems at odds with the large unfavorable desolvation free energy reported for tetramethylammonium (TMA+), a frequently utilized surrogate of methonium. Using a combination of experimental and computational studies, we show that the transfer of methonium from bulk water (partially solvated methonium state) to the CB[7] cavity (mostly desolvated methonium state) is accompanied by a remarkably small desolvation enthalpy of just 0.5 ± 0.3 kcal•mol–1, a value significantly less endothermic than those values suggested from gas-phase model studies

Zeolites

Effects of amine organic groups as lattice in ZSM-5 on the hydrolysis of dimethyl ether

Jittima Meepraserta, Siriporn Jungsuttiwongb, Thanh N. Truongc, Supawadee Namuangruka,[Technology Development Agency, Klong Luang] ,

J. Mol.Graph. and Mod., **42** 31–40, 2013.

The effects of doping amine to ZSM-5 on its catalytic activity for hydrolysis of dimethyl ether (DME) have been studied theoretically using Density Functional Theory with the embedded cluster ONIOM(M06/6-31G(d,p):UFF) model. Doping by amine to ZSM-5 yields two new active centers, namely the protonated Z[NH2] and non-protonated Z[NH] amine sites in addition to the normal Brønsted acid Z[OH] site. The reaction has two possible stepwise and concerted channels. The stepwise channel consists of two elementary steps; (i) the demethylation followed by (ii) the hydrolysis while the concerted channel involves in the demethylation and hydrolysis in a single step.

Carbon Nanoparticles

Torsional Forces Mediated by Surfactant Aggregates on Carbon Nanotube Junctions

Dirk Müter[Heriot-Watt University] and Henry Bock

J. Phys. Chem. B., **117**, 5585–5593, 2013**.**

Surfactant-mediated interactions acting along the line of shortest contact between carbon nanotubes have been investigated by many authors, but the surfactant-mediated torsion that arises in the case of angled tubes have so far been ignored. Here we show for the first time that a strong torsional force originates from the central surfactant aggregate that forms at the crossing between nonparallel nanotubes. Our dissipative particle dynamics simulations demonstrate that this torque pulls the tubes into a parallel arrangement.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

The Simmune Modeler visual interface for creating signaling networks based on bi-molecular interactions

Fengkai Zhang, Bastian R. Angermann and Martin Meier-Schellersheim[National Institute of Allergy and Infectious Diseases]

Bioinformatics. **29**, 1229-1230, 2013.

Biochemical modeling efforts now frequently take advantage of the possibility to automatically create reaction networks based on the specification of pairwise molecular interactions. Even though a variety of tools exist to visualize the resulting networks, defining the rules for the molecular interactions typically requires writing scripts, which impacts the non-specialist accessibility of those approaches. We introduce the Simmune Modeler that allows users to specify molecular complexes and their interactions as well as the reaction-induced modifications of the molecules through a flexible visual interface.

Bioinformatics and Molecular Dynamics Simulation Study of L1 Stalk Non-Canonical rRNA Elements: Kink-Turns, Loops, and Tetraloops

Miroslav Krepl, Kamila Réblová, Jaroslav Koča, and Jiří Šponer [Campus Bohunice,]

J. Phys. Chem. B., **117**, 5540–5555, 2013**.**

The L1 stalk is a prominent mobile element of the large ribosomal subunit. We explore the structure and dynamics of its non-canonical rRNA elements, which include two kink-turns, an internal loop, and a tetraloop. We use bioinformatics to identify the L1 stalk RNA conservation patterns and carry out over 11.5 μs of MD simulations for a set of systems ranging from isolated RNA building blocks up to complexes of L1 stalk rRNA with the L1 protein and tRNA fragment. We show that the L1 stalk tetraloop has an unusual GNNA or UNNG conservation pattern deviating from major GNRA and YNMG RNA tetraloop families.

Protein Confirmational Analysis

Parametric Bayesian priors and better choice of negative examples improve protein function prediction

Noah Youngs, Duncan Penfold-Brown, Kevin Drew, Dennis Shasha [New York University], and Richard Bonneau

Bioinformatics. **29**, 1190-1198, 2013.

Computational biologists have demonstrated the utility of using machine learning methods to predict protein function from an integration of multiple genome-wide data types. Yet, even the best performing function prediction algorithms rely on heuristics for important components of the algorithm, such as choosing negative examples (proteins without a given function) or determining key parameters. The improper choice of negative examples, in particular, can hamper the accuracy of protein function prediction. We present a novel approach for choosing negative examples, using a parameterizable Bayesian prior computed from all observed annotation data, which also generates priors used during function prediction.

Mapping Conformational Dynamics of Proteins Using Torsional Dynamics Simulations

Vamshi K. Gangupomu, Jeffrey R. Wagner, In-Hee Park, Abhinandan Jain, Nagarajan Vaidehi[Beckman Research Institute of the City of Hope] ,

Biophysical Journal. **104**, 1999-2008, 2013.

All-atom molecular dynamics simulations are widely used to study the flexibility of protein conformations. However, enhanced sampling techniques are required for simulating protein dynamics that occur on the millisecond timescale. In this work, we show that torsional molecular dynamics simulations enhance protein conformational sampling by performing conformational search in the low-frequency torsional degrees of freedom. we use our recently developed torsional-dynamics method called Generalized Newton-Euler Inverse Mass Operator (GNEIMO) to study the conformational dynamics of four proteins.

Labeling Proteins with Fluorophore/Thioamide Förster Resonant Energy Transfer Pairs by Combining Unnatural Amino Acid Mutagenesis and Native Chemical Ligation

Rebecca F. Wissner , Solongo Batjargal , Colin M. Fadzen , and E. James Petersson[niversity of Pennsylvania]

J. Am. Chem. Soc., 2013, **135**, 6529–6540

We have recently shown that p-cyanophenylalanine (Cnf) and a thioamide can be used as a minimally perturbing Förster resonant energy transfer (FRET) pair to monitor protein conformation. We have also shown that thioamide analogues of natural amino acids can be incorporated into full-sized proteins through native chemical ligation. For intermolecular studies with Cnf/thioamide FRET pairs, Cnf can be incorporated into proteins expressed inEscherichia coli through unnatural amino acid mutagenesis using a Cnf-specific tRNA synthetase.

Protein Confirmational Analysis (Cont'd)

Conformational analysis of lignin models: a chemometric approach

Eduardo W. Castilho-Almeida[Universidade Federal de Juiz de For a], Wagner B. De Almeida, Hélio F. Dos Santos

J. Mol.Mod., **19,** 2149-2163, 2013.

In the present work, conformational analysis of lignin models was accomplished by considering four cross-link types (3–5′, β-5′, α-O-4 and β-O-4) and three monomer units [guaiacyl (G), p-hydroxyphenyl (H) and syringyl (S)]. Analysis involving the 3–5′ and β-5′ dimers was conducted following the standard procedure, i.e., rotating the monomers around the single bond. On the other hand, analysis of α-O-4 and β-O-4 dimers followed a distinct protocol with the aid of an interesting chemometric tool called Box-Behnken (BB) design.

Conformational Entropy of Intrinsically Disordered Protein

Song-Ho Chong and Sihyun Ham[Sookmyung Women's University]

J. Phys. Chem. B., **117**, 3271–3279, 2013**.**

Intrinsically disordered proteins (IDPs), though lacking stable tertiary structures, are known to possess a certain amount of residual structure. Conformational disorder plays a crucial role through the conformational entropy in regulating protein–protein and protein–ligand interactions involved in signaling and regulation, and also modulates protein aggregation and amyloidogenesis associated with a number of human diseases. Here we show using a novel computational approach that the conformational entropy of amyloid-beta protein, an IDP whose aggregation is associated with Alzheimer's disease, is significantly correlated with the contents of the residual helical structure, β-sheet structure, and salt-bridge network.

Conformational Ensemble and Polymorphism of the All-Atom Alzheimer's Aβ37–42 Amyloid Peptide Oligomers

Phuong H. Nguyen and Philippe Derreumaux [Institut Universitaire de France]

J. Phys. Chem. B., **117**, 5831–5840, 2013**.**

A!

Although the Aβ37–42 peptide has two opposite terminal charges, counterintuitively its current fibril amyloid structure reveals in register parallel β-strands, as formed by the full length Aβ peptide. In this study, we carried out a replica exchange molecular dynamics simulation of 16 all-atom Aβ37–42 peptides in explicit water starting from randomized and dispersed chains. The extensive conformational sampling (48 replicas, 460 ns/replica) with a total simulation time of 23 μs allows us to obtain a full picture on the equilibrium conformational distribution of oligomers and β-sheet sizes and gain some insights into the oligomerization process at 300 K.

Effects of protonation state of Asp181 and position of active site water molecules on the conformation of PTP1B

Ahmet Özcan, Elif Ozkirimli Olmez and Burak Alakent[Bogazici University]

Proteins: Stru. Fun. & Bioinf., **81**, 788–804, 2013.

A!

In protein tyrosine phosphatase 1B (PTP1B), the flexible WPD loop adopts a closed conformation (WPDclosed) in the active state of PTP1B, bringing the catalytic Asp181 close to the active site pocket, while WPD loop is in an open conformation (WPDopen) in the inactive state. Previous studies showed that Asp181 may be protonated at physiological pH, and ordered water molecules exist in the active site. In the current study, molecular dynamics simulations are employed at different Asp181 protonation states and initial positions of active site water molecules, and compared with the existing crystallographic data of PTP1B.

Protein Structure Analysis

Molecular dynamics simulation studies of the structural response of an isolated Aβ1–42monomer localized in the vicinity of the hydrophilic TiO2 surface

Jaya C. Jose, Neelanjana Sengupta[CSIR-National Chemical Laboratory,]

Euro.biophy. jour., **42**, 487-494, 2013.

We have probed the effect of a model hydrophilic surface, rutile TiO2, on the full-length amyloid beta (Aβ1–42) monomer using molecular dynamics simulations. The rutile surface brings about sharp changes in the peptide's intrinsic behavior in a distance-dependent manner. The intrinsic collapse of the peptide is disrupted, while the β-sheet propensity is sharply enhanced with increased proximity to the surface. The results may have implications for Aβ self-assembly and fibrillogenesis on hydrophilic surfaces and should be taken into consideration in the design of novel nanomaterials for perturbing amyloidogenic behavior.

A Mixed Protein Structure Network and Elastic Network Model Approach to Predict the Structural Communication in Biomolecular Systems: The PDZ2 Domain from Tyrosine Phosphatase 1E As a Case Study

Francesco Raimondi , Angelo Felline , Michele Seeber , Simona Mariani , and Francesca Fanelli [Department of Life Sciences, Modena]

J. Chem. Theor. and Comp, **9**, 2504–2518, 2013.

We propose a mixed Protein Structure Network (PSN) and Elastic Network Model (ENM)-based strategy, i.e., PSN-ENM, for fast investigation of allosterism in biological systems. PSN analysis and ENM-Normal Mode Analysis (ENM-NMA) are implemented in the structural analysis software Wordom, freely available at http://wordom.sourceforge.net/. The method performs a systematic search of the shortest communication pathways that traverse a protein structure.

Protein Dynamics

A Perfluoroaryl-Cysteine SNAr Chemistry Approach to Unprotected Peptide Stapling

Alexander M. Spokoyny , Yekui Zou , Jingjing J. Ling , Hongtao Yu , Yu-Shan Lin , and Bradley L. Pentelute [Massachusetts Institute of Technology]

J. Am. Chem. Soc., 2013, **135**,4372–4379

We report the discovery of a facile transformation between perfluoroaromatic molecules and a cysteine thiolate, which is arylated at room temperature. This new approach enabled us to selectively modify cysteine residues in unprotected peptides, providing access to variants containing rigid perfluoroaromatic staples. This stapling modification performed on a peptide sequence designed to bind the C-terminal domain of an HIV-1 capsid assembly polyprotein (C-CA) showed enhancement in binding, cell permeability, and proteolytic stability properties.

A Mechanistic Model for Amorphous Protein Aggregation of Immunoglobulin-like Domains

Madeleine B. Borgia , Adrian A. Nickson , Jane Clarke , and Michael J. Hounslow [University of Sheffield]

J. Am. Chem. Soc., 2013, **135**, 6456–6464

Protein aggregation is associated with many debilitating diseases including Alzheimer's, Parkinson's, and light-chain amyloidosis (AL). Additionally, such aggregation is a major problem in an industrial setting where antibody therapeutics often require high local concentrations of protein domains to be stable for substantial periods of time. However, despite a plethora of research in this field, dating back over 50 years, there is still no consensus on the mechanistic basis for protein aggregation. We use experimental data to derive a mechanistic model that well describes the aggregation of Titin I27, an immunoglobulin-like domain.

Protein Dynamics (Cont'd)

Decrypting Prion Protein Conversion into a β-Rich Conformer by Molecular Dynamics

Nesrine Chakroun , Arianna Fornili , Stéphanie Prigent , Jens Kleinjung , Cécile A. Dreiss ,Human Rezaei , and Franca Fraternali [King's College London]

J. Chem. Theor. and Comp, **9**, 2455–2465, 2013.

Prion diseases are fatal neurodegenerative diseases characterized by the formation of β-rich oligomers and the accumulation of amyloid fibrillar deposits in the central nervous system. Understanding the conversion of the cellular prion protein into its β-rich polymeric conformers is fundamental to tackling the early stages of the development of prion diseases. In this paper, we have identified unfolding and refolding steps critical to the conversion into a β-rich conformer for different constructs of the ovine prion protein by MD simulations.

Self-Assembly of Gemini Surfactants: A Computer Simulation Study

Jagannath Mondal, Mahesh Mahanthappa, and Arun Yethiraj [University of Wisconsin]

J. Phys. Chem. B., **117**, 4254–4262, 2013**.**

The self-assembly behavior of gemini (dimeric or twin-tail) dicarboxylate disodium surfactants is studied using MD simulations. A united atom model is employed for the surfactants with fully atomistic counterions and water. This gemini architecture, in which two single tailed surfactants are joined through a flexible hydrophobic linker, has been shown to exhibit concentration-dependent aqueous self-assembly into lyotropic phases including hexagonal, gyroid, and lamellar morphologies. Our simulations reproduce the experimentally observed phases at similar amphiphile concentrations in water, including the unusual ability of these surfactants to form gyroid phases over unprecedentedly large amphiphile concentration windows.

Theoretical Elucidation of the Origin for Assembly of the DAP12 Dimer with Only One NKG2C in the Lipid Membrane

Hui Sun, Huiying Chu, Ting Fu, Hujun Shen, and Guohui Li [Chinese Academy of Sciences,]

J. Phys. Chem. B., **117**, 4789–4797, 2013**.**

In this work, we have investigated in details the origin of the assembly of the DAP12 dimer with only one NKG2C in the activating immunoreceptor complex from thew two aspects of electronic properties and dynamic structures by performing density functional theory (DFT) calculations and molecular dynamics (MD) simulations. In the DFT calculations, we studied the aggregation ability of the NKG2CTM with the DAP12TM dimer and the DAP12TM–DAP12TM–NKG2CTM complex by analyzing the electrostatic potentials and frontier molecular orbitals (FMOs), and in the MD simulations we mainly investigated the dynamic structures of the DAP12TM–DAP12TM–NKG2CTM complex and its mutants.

Direct Evidence for Hydrogen Bonding in Glycans: A Combined NMR and Molecular Dynamics Study

Marcos D. Battistel, Robert Pendrill, Göran Widmalm, and Darón I. Freedberg [Center for Biologics Evaluation and Research, Rockville]

J. Phys. Chem. B., **117**, 4860–4869, 2013**.**

We introduce the abundant hydroxyl groups of glycans as NMR handles and structural probes to expand the repertoire of tools for structure–function studies on glycans in solution. To this end, we present the facile detection and assignment of hydroxyl groups in a wide range of sample concentrations (0.5–1700 mM) and temperatures, ranging from −5 to 25 °C. We then exploit this information to directly detect hydrogen bonds, well-known for their importance in molecular structural determination through NMR.

A!

Protein Dynamics (Cont'd)

The Stabilization Effect of Dielectric Constant and Acidic Amino Acids on Arginine–Arginine (Arg–Arg) Pairings: Database Survey and Computational Studies

Zhengyan Zhang , Zhijian Xu , Zhuo Yang ,Yingtao Liu , Jin'an Wang , Qiang Shao , Shujin Li , Yunxiang Lu , and Weiliang Zhu [Soochow University]

J. Phys. Chem. B., **117**, 4827–48359, 2013**.**

Database survey in this study revealed that about one-third of the protein structures deposited in the Protein Data Bank (PDB) contain arginine–arginine (Arg–Arg) pairing with a carbon•••carbon (CZ•••CZ) interaction distance less than 5 Å. All the Arg–Arg pairings were found to bury in a polar environment composed of acidic residues, water molecules, and strong polarizable or negatively charged moieties from binding site or bound ligand. Most of the Arg–Arg pairings are solvent exposed and 68.3% Arg–Arg pairings are stabilized by acidic residues, forming Arg–Arg–Asp/Glu clusters.

On the Foldability of Tryptophan-Containing Tetra- and Pentapeptides: An Exhaustive Molecular Dynamics Study

Panagiota S. Georgoulia and Nicholas M. Glykos[Democritus University of Thrace

J. Phys. Chem. B., **117**, 5522–5532, 2013**.**

A!

Short peptides serve as minimal model systems to decipher the determinants of foldability due to their simplicity arising from their smaller size, their ability to echo protein-like structural characteristics, and their direct implication in force field validation. Here, we describe an effort to identify small peptides that can still form stable structures in aqueous solutions. We followed the in silico folding of a selected set of 8640 tryptophan-containing tetra- and pentapeptides through 15 210 molecular dynamics simulations amounting to a total of 272.46 μs using explicit representation of the solute and full treatment of the electrostatics.

Exploring the Molecular Mechanism of Trimethylamine-N-oxide's Ability to Counteract the Protein Denaturing Effects of Urea

Rahul Sarma and Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **117**, 5691–5704, 2013**.**

Protein denaturation in highly concentrated urea solution is a well-known phenomenon. The counteracting effect of a naturally occurring osmolyte, trimethylamine-N-oxide (TMAO), against urea-conferred protein denaturation is also well-established. However, what is largely unknown is the mechanism by which TMAO counteracts this denaturation. To provide a molecular level understanding of how TMAO protects proteins in highly concentrated urea solution, we report here the structural, energetic, and dynamical properties of N-methylacetamide (NMA) solutions that also contain urea and/or TMAO.

Effect of Asphaltene Structure on Association and Aggregation Using Molecular Dynamics

Mohammad Sedghi, Lamia Goual [University of Wyoming], William Welch, and Jan Kubelka

J. Phys. Chem. B., **117**, 5765–5776, 2013**.**

The aggregation of asphaltenes has been established for decades by numerous experimental techniques; however, very few studies have been performed on the association free energy and asphaltene aggregation in solvents. The lack of reliable and coherent data on the free energy of association and aggregation size of asphaltene has imposed severe limitations on the thermodynamic modeling of asphaltene phase behavior. In this work, the relations between Gibbs free energy of asphaltene association and asphaltene molecular structure are studied using molecular dynamics (MD).

Protein Dynamics (Cont'd)

Study of Q224K, V152G double mutation in bean PGIP2, an LRR protein for plant defense—An in silico approach

Aditi Maulik and Soumalee Basu[West Bengal University of Technology]

Proteins: Stru. Fun. & Bioinf., **81**, 852–862, 2013.

Polygalacturonase inhibiting proteins (PGIPs) are leucine-rich repeat (LRR) proteins from plants that are organized into multigene families. They act as specific inhibitors against Polygalacturonases (PGs) from phytopathogens and share high sequence identity within species. We performed in silico mutation (Q224K and V152G) in PGIP2 from Phaseolus vulgaris to corresponding residues of another member, PGIP1. This mutation is known to cause 100% loss of inhibition against the PG of fungus Fusarium phyllophilum (Fp). A comparative analysis between PGIP2 and the double mutant, using 50 ns molecular dynamics simulations explored structural difference affecting PG binding properties.

Quaternary structure effects on the hexacoordination equilibrium in rice hemoglobin rHb1: Insights from molecular dynamics simulations

Uriel N. Morzan, Luciana Capece,Marcelo A. Marti [Universidad de Buenos Aires],Dario A. Estrin

Proteins: Stru. Fun. & Bioinf., **81**, 863–873, 2013.

Nonsymbiotic hemoglobins (nsHbs) form a widely distributed class of plant proteins, which function remains unknown. Despite the fact that class 1 plant nonsymbiotic hemoglobins are hexacoordinate (6c) heme proteins (hxHbs), their hexacoordination equilibrium constants are much lower than in hxHbs from animals or bacteria. In addition, they are characterized by having very high oxygen affinities and low oxygen dissociation rate constants. Rice hemoglobin 1 (rHb1) is a class 1 nonsymbiotic hemoglobin. In this work, we analyze the molecular basis that determine the hexacoordination equilibrium in rHb1. Our results indicate that dynamical features of the quaternary structure significantly affect the hexacoordination process.

Free Energy Calculations

Comparison of thermodynamic integration and Bennett's acceptance ratio for calculating relative protein-ligand binding free energies

Anita de Ruiter, Stefan Boresch, Chris Oostenbrink[BOKU – University of Natural Resources and Life Sciences, Muthgasse]

J. Comp. Chem., **34**, 1024–1034, 2013.

The performances of Bennett's acceptance ratio method and thermodynamic integration (TI) for the calculation of free energy differences in protein simulations are compared. For the latter, the standard trapezoidal rule, Simpson's rule, and Clenshaw-Curtis integration are used as numerical integration methods. We evaluate the influence of the number and definition of intermediate states on the precision, accuracy, and efficiency of the free energy calculations.

Ligand Binding/Docking

Determination of the α-Conotoxin Vc1.1 Binding Site on the α9α10 Nicotinic Acetylcholine Receptor

Rilei Yu, Shiva N. Kompella, David J. Adams, David J. Craik, and Quentin Kaas[University of Queensland]

J.Med.Chem., **56,** 3557–3567, 2013.

α-Conotoxin Vc1.1 specifically and potently inhibits the nicotinic acetylcholine receptor subtype α9α10 (α9α10 nAChR) and is a potential novel treatment for neuropathic pain. Here, we used a combination of computational modeling and electrophysiology experiments to determine the Vc1.1 binding site on the α9α10 nAChR. Interactions of Vc1.1 with two probable binding sites, α9α10 and α10α9, were modeled. Mutational energies calculated by assuming specific interactions in the α10α9 binding site correlated better with electrophysiological recordings than those assuming interactions with the α9α10 binding site

Enzyme Catalysis

Differential Role of the Protein Matrix on the Binding of a Catalytic Aspartate to Mg2+ vs Ca2+: Application to Ribonuclease H

C. Satheesan Babu, Todor Dudev, and Carmay Lim [National Tsing Hua University]

J. Am. Chem. Soc., 2013, **135**, 6541–6548

A!

Divalent metal cations are essential cofactors for many enzyme functions. Although Mg2+ is the native cofactor in many enzymes such as ribonuclease H, its competitor Ca2+ may also bind to the enzyme but inhibit catalysis. Thus, the competition between Mg2+ and Ca2+ for a given metal-binding site in an enzyme and their effects on enzyme activity are of great interest. Most studies have focused on the interactions between Mg2+ or Ca2+ and the metal ligands in the first and sometimes second coordination shell. In this work, the free energy barriers for the binding of a catalytically essential aspartate to Mg2+ or Ca2+ in ribonuclease H from two organisms were computed using umbrella sampling with a classical force field ("classical" model).

Unraveling the Enigmatic Mechanism of l-Asparaginase II with QM/QM Calculations

Diana S. Gesto, Nuno M. F. S. A. Cerqueira, Pedro A. Fernandes, and Maria J. Ramos [Sciences Faculty of Porto University]

J. Am. Chem. Soc., 2013, **135**, 7146–7158

In this paper, we have studied the catalytic mechanism of L-asparaginase II computationally. The reaction mechanism was investigated using the ONIOM methodology. For the geometry optimization we used the B3LYP/6-31G(d):AM1 level of theory, and for the single points we used the M06-2X/6-311++G(2d,2p):M06-2X/6-31G(d) level of theory. It was demonstrated that the full mechanism involves three sequential steps and requires the nucleophilic attack of a water molecule on the substrate prior to the release of ammonia. There are three rate-limiting states, which are the reactants, the first transition state, and the last transition state

Enzyme Catalysis (Cont'd)

Aminoacyl-tRNA Substrate and Enzyme Backbone Atoms Contribute to Translational Quality Control by YbaK

Sandeep Kumar, Mom Das, Christopher M. Hadad, and Karin Musier-Forsyth [The Ohio State University]

J. Phys. Chem. B., **117**, 4521–4527, 2013**.**

A!

Amino acids are covalently attached to their corresponding transfer RNAs (tRNAs) by aminoacyl-tRNA synthetases. Proofreading mechanisms exist to ensure that high fidelity is maintained in this key step in protein synthesis. Prolyl-tRNA synthetase (ProRS) can misacylate cognate tRNAPro with Ala and Cys. The cis-editing domain of ProRS (INS) hydrolyzes Ala-tRNAPro, whereas Cys-tRNAPro is hydrolyzed by a single domain editing protein, YbaK, in trans. Previous studies have proposed a model of substrate-binding by bacterial YbaK and elucidated a substrate-assisted mechanism of catalysis.

Protein-Protein Interactions

PeptideLocator: prediction of bioactive peptides in protein sequences

Catherine Mooney, Niall J. Haslam, Thérèse A. Holton, Gianluca Pollastri, and Denis C. Shields[University College Dublin]

Bioinformatics. **29**, 1120-1126, 2013.

Peptides play important roles in signalling, regulation and immunity within an organism. Many have successfully been used as therapeutic products often mimicking naturally occurring peptides. We present PeptideLocator for the automated prediction of functional peptides in a protein sequence. We have trained a machine learning algorithm to predict bioactive peptides within protein sequences. PeptideLocator performs well on training data achieving an area under the curve of 0.92 when tested in 5-fold cross-validation on a set of 2202 redundancy reduced peptide containing protein sequences.

Specificity and affinity quantification of protein–protein interactions

Zhiqiang Yan, Liyong Guo, Liang Hu and Jin Wang[State University of New York at Stony Brook]

Bioinformatics. **29**, 1127-1133, 2013.

Determination of the protein–protein structures and insight into their interactions are vital to understand the mechanisms of protein functions. Currently, compared with the isolated protein structures, only a small fraction of protein–protein structures are experimentally solved. We developed a scoring function (named as SPA-PP, specificity and affinity of the protein–protein interactions) by incorporating both the specificity and affinity into the optimization strategy. The testing results and comparisons with other scoring functions show that SPA-PP performs remarkably on both predictions of binding pose and binding affinity.

Comprehensive Experimental and Computational Analysis of Binding Energy Hot Spots at the NF-κB Essential Modulator/IKKβ Protein–Protein Interface

Mary S. Golden , Shaun M. Cote , Marianna Sayeg, Brandon S. Zerbe , Elizabeth A. Villar , Dmitri Beglov , Stephen L. Sazinsky , Rosina M. Georgiadis , Sandor Vajda , Dima Kozakov , and Adrian Whitty [Boston University]

J. Am. Chem. Soc., 2013, **135,**6242–6256

We report a comprehensive analysis of binding energy hot spots at the protein–protein interaction interface between nuclear factor kappa B essential modulator (NEMO) and IκB kinase subunit β (IKKβ), an interaction that is critical for NF-κB pathway signaling, using experimental alanine scanning mutagenesis and also the FTMap method for computational fragment screening. The experimental results confirm that the previously identified NEMO binding domain (NBD) region of IKKβ contains the highest concentration of hot-spot residues, the strongest of which are W739, W741, and L742.

Protein-Protein Interactions (Cont'd)

Quantum-Chemical Electron Densities of Proteins and of Selected Protein Sites from Subsystem Density Functional Theory

Karin Kiewisch, Christoph R. Jacob, and Lucas Visscher [VU University Amsterdam]

J. Chem. Theor. and Comp, **9**, 2425–2440, 2013.

The ability to calculate accurate electron densities of full proteins or of selected sites in proteins is a prerequisite for a fully quantum-mechanical calculation of protein–protein and protein–ligand interaction energies. Quantum-chemical subsystem methods capable of treating proteins and other biomolecular systems provide a route to calculate the electron densities of proteins efficiently and further make it possible to focus on specific parts. Here, we evaluate and extend the 3-partition frozen-density embedding (3-FDE) scheme [Jacob, C. R.; Visscher, L. J. Chem. Phys.2008, 128, 155102] for this purpose.

Calculating the Bimolecular Rate of Protein–Protein Association with Interacting Crowders

Eng-Hui Yap and Teresa Head-Gordon [University of California]

J. Chem. Theor. and Comp, **9**, 2481–2489, 2013.

We have recently introduced a method termed Poisson–Boltzmann semianalytical method (PB-SAM) for solving the linearized Poisson–Boltzmann equation for large numbers of arbitrarily shaped dielectric cavities with controlled precision. In this work we extend the applicability of the PB-SAM approach by deriving force and torque expressions that fully account for mutual polarization in both the zero- and first-order derivatives of the surface charges, that can now be embedded into a Brownian dynamics scheme to look at electrostatic-driven mesoscale assembly and kinetics.

Insight into structural and biochemical determinants of substrate specificity of PFI1625c: Correlation analysis of protein-peptide molecular models

Kimjolly Lhouvuma, Vibin Ramakrishnanb, Vishal Trivedia [Indian Institute of Technology-Guwahati],

J. Mol.Graph. and Mod., **42** 21–30, 2013.

Bioinformatics and sequence comparison indicate PFI1625c as a putative metalloprotease present in plasmodium genome. The structure of PFI1625c consists of two domains with nearly identical folding topology. The active site of PFI1625c is located in a large central cavity between the two domains. Substrate binding regions of PFI1625c are lined by E-136, D-140 which provides negatively charged patches whereas F-53 facilitates binding of bulky hydrophobic residues of substrates. Probing PFI1625c active site with 199 different peptides from a combinatorial peptide library indicates preference of PFI1626c toward hydrophobic residue substituted peptides.

Predicting permanent and transient protein–protein interfaces

David La,Misun Kong, William Hoffman, Youn Im Choi,Daisuke Kihara,[Purdue University]

Proteins: Stru. Fun. & Bioinf., **81**, 805–818, 2013.

Protein–protein interactions (PPIs) are involved in diverse functions in a cell. To optimize functional roles of interactions, proteins interact with a spectrum of binding affinities. Interactions are conventionally classified into permanent and transient, where the former denotes tight binding between proteins that result in strong complexes, whereas the latter compose of relatively weak interactions that can dissociate after binding to regulate functional activity at specific time point. In this study, we constructed amino acid substitution models that capture mutation patterns at permanent and transient type of protein interfaces, which were found to be different with statistical significance.

Membrane Proteins and Lipid Peptide Interactions

Protein-specific force field derived from the fragment molecular orbital method can improve protein–ligand binding interactions

Le Chang, Takeshi Ishikawa, Kazuo Kuwata, Shoji Takada[Kyoto University]

J. Comp. Chem., **34**, 1251–1257, 2013.

Accurate computational estimate of the protein–ligand binding affinity is of central importance in rational drug design. To improve accuracy of the molecular mechanics (MM) force field (FF) for protein–ligand simulations, we use a protein-specific FF derived by the fragment molecular orbital (FMO) method and by the restrained electrostatic potential (RESP) method. Applying this FMO-RESP method to two proteins, dodecin, and lysozyme, we found that protein-specific partial charges tend to differ more significantly from the standard AMBER charges for isolated charged atoms.

Validation of Depth-Dependent Fluorescence Quenching in Membranes by Molecular Dynamics Simulation of Tryptophan Octyl Ester in POPC Bilayer

Alexander Kyrychenko , Douglas J. Tobias , andAlexey S. Ladokhin [University Medical Center, Kansas City]

J. Phys. Chem. B., **117**, 4770–4778, 2013**.**

A!

Depth-dependent fluorescence quenching is an important tool for studying the penetration of proteins and peptides into lipid bilayers. Extracting quantitative information from quenching data is, however, complicated by (1) a limited number of experimentally available quenchers and (2) thermal disorder resulting in broad distributions of the transverse positions of both quenchers and fluorophores. Here we validate and refine a general approach to determining the location of a fluorescent probe along the bilayer normal from quenching data, based on a MD simulation of a model compound, tryptophan octyl ester (TOE), in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) bilayer.

Limited Perturbation of a DPPC Bilayer by Fluorescent Lipid Probes: A Molecular Dynamics Study

David G. Ackerman , Frederick A. Heberle , andGerald W. Feigenson [Genetics,Cornell University]

J. Phys. Chem. B., **117**, 4844–4852, 2013**.**

The properties of lipid bilayer nanometer-scale domains could be crucial for understanding cell membranes. Fluorescent probes are often used to study bilayers, yet their effects on host lipids are not well understood. We used molecular dynamics simulations to investigate perturbations in a fluid DPPC bilayer upon incorporation of three indocarbocyanine probes: DiI-C18:0, DiI-C18:2, or DiI-C12:0. We find a 10–12% decrease in chain order for DPPC in the solvation shell nearest the probe but smaller effects in subsequent shells, indicating that the probes significantly alter only their local environment.

Molecular Dynamics Simulations of DPPC Bilayers Using "LIME", a New Coarse-Grained Model

Emily M. Curtis and Carol K. Hall [North Carolina State University]

J. Phys. Chem. B., **117**, 5019–5030, 2013**.**

A new intermediate resolution model for phospholipids, LIME, designed for use with discontinuous molecular dynamics (DMD) simulations is presented. The implicit-solvent model was developed using a multiscale modeling approach in which the geometric and energetic parameters are obtained by collecting data from atomistic simulations of a system composed of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) molecules and explicit water. In the model, 14 coarse-grained sites that are classified as 1 of 6 types represent DPPC.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Melittin Creates Transient Pores in a Lipid Bilayer: Results from Computer Simulations

Kolattukudy P. Santo, Sheeba J. Irudayam, and Max L. Berkowitz[University of North Carolina at Chapel Hill]

J. Phys. Chem. B., **117**, 5031–5042, 2013**.**

To study the interaction between melittin peptides and lipid bilayer, we performed coarse-grained simulations on systems containing melittin interacting with a bilayer containing zwitterionic dipalmitoylphosphatidylcholine (DPPC) and anionic palmitoyloleoylphosphatidylglycerol (POPG) phospholipids in a 7:3 ratio. Eight different systems were considered: four at low and four at high peptide to lipid (P/L) ratios. In case of low P/L ratio we did not observe any pore creation in the bilayer.

Comparing Simulations of Lipid Bilayers to Scattering Data: The GROMOS 43A1-S3 Force Field

Anthony R. Braun, Jonathan N. Sachs, and John F. Nagle[Carnegie Mellon University]

J. Phys. Chem. B., **117**, 5065–5072, 2013**.**

Simulations of DOPC at T = 303 K were performed using the united atom force field 43A1-S3 at six fixed projected areas, AP = 62, 64, 66, 68, 70, and 72 Å2, as well as a tensionless simulation that produced an average ANPT = 65.8 Å2. After a small undulation correction for the system size consisting of 288 lipids, results were compared to experimental data. The best, and excellent, fit to neutron scattering data occurs at an interpolated AN = 66.6 Å2 and the best, but not as good, fit to the more extensive X-ray scattering data occurs at AX = 68.7 Å2.

Driving Force for Crystallization of Anionic Lipid Membranes Revealed by Atomistic Simulations

Bao Fu Qiao and Monica Olvera de la Cruz [Northwestern University]

J. Phys. Chem. B., **117**, 5073–5080, 2013**.**

Crystalline vesicles are promising nanomaterials due to their mechanical stability in various environments. To control their fabrication, it is essential to understand the effects of different experimental conditions on crystallization. Here we perform atomistic molecular dynamics simulations of anionic lipid membranes of 1,2-dilauroyl-sn-glycero-3-phosphol-L-serine. In the presence of Na+ monovalent counterions, we access the phase transition from the liquid-like disordered liquid-crystalline phase to the ordered gel phase by lowering the temperature of the system.

Behavior of Fluorescent Cholesterol Analogues Dehydroergosterol and Cholestatrienol in Lipid Bilayers: A Molecular Dynamics Study

João R. Robalo, António M. T. Martins do Canto, A. J. Palace Carvalho, J. P. Prates Ramalho, and Luís M. S. Loura [Universidade de Coimbra,]

J. Phys. Chem. B., **117**, 5806–5819, 2013**.**

MD simulations of bilayer systems consisting of varying proportions of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), cholesterol (Chol), and intrinsically fluorescent Chol analogues dehydroergosterol or cholestatrienol (CTL) were carried out to study in detail the extent to which these fluorescent probes mimic Chol's behavior (location, orientation, dynamics) in membranes as well as their effect on host bilayer structure and dynamics (namely their ability to induce membrane ordering in comparison with Chol).

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulations of Depth Distribution of Spin-Labeled Phospholipids within Lipid Bilayer

Alexander Kyrychenko[Kansas University Medical Center] and Alexey S. Ladokhin

J. Phys. Chem. B., **117**, 5875–5885, 2013**.**

Spin-labeled lipids are commonly used as fluorescence quenchers in studies of membrane penetration of dye-labeled proteins and peptides using depth-dependent quenching. Accurate calculations of depth of the fluorophore rely on the use of several spin labels placed in the membrane at various positions. In this Article, we use molecular dynamics (MD) simulations to study the membrane behavior and depth distributions of spin-labeled phospholipids in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) bilayer.

Predicting Ligand Binding Modes from Neural Networks Trained on Protein–Ligand Interaction Fingerprints

Vladimir Chupakhin , Gilles Marcou , Igor Baskin, Alexandre Varnek , and Didier Rognan[UMR 7200University of Strasbourg/CNRS]

J.Chem. Infor. and Mod. **53**, 763–772, 2013.

We herewith present a novel approach to predict protein–ligand binding modes from the single two-dimensional structure of the ligand. Known protein–ligand X-ray structures were converted into binary bit strings encoding protein–ligand interactions. An artificial neural network was then set up to first learn and then predict protein–ligand interaction fingerprints from simple ligand descriptors. Specific models were constructed for three targets (CDK2, p38-α, HSP90-α) and 146 ligands for which protein–ligand X-ray structures are available. These models were able to predict protein–ligand interaction fingerprints and to discriminate important features from minor interactions.

Protein Folding

Evaluation of Dimensionality-Reduction Methods from Peptide Folding–Unfolding Simulations

Mojie Duan , Jue Fan , Minghai Li , Li Han , and Shuanghong Huo[Clark University]

J. Chem. Theor. and Comp, **9**, 2490–2497, 2013.

A!

Dimensionality-reduction methods have been widely used to study the free energy landscapes and low-free-energy pathways of molecular systems. It was shown that the nonlinear dimensionality-reduction methods gave better embedding results than the linear methods, such as principal component analysis, in some simple systems. In this study, we have evaluated several nonlinear methods, locally linear embedding, Isomap, and diffusion maps, as well as principal component analysis from the equilibrium folding/unfolding trajectory of the second β-hairpin of the B1 domain of streptococcal protein G.

Chemical Unfolding of Chicken Villin Headpiece in Aqueous Dimethyl Sulfoxide Solution: Cosolvent Concentration Dependence, Pathway, and Microscopic Mechanism

Susmita Roy and Biman Bagchi[Indian Institute of Science, Bangalore]

J. Phys. Chem. B., **117**, 4488–4502, 2013**.**

Unfolding of a protein often proceeds through partial unfolded intermediate states (PUIS). PUIS have been detected in several experimental and simulation studies. However, complete analyses of transitions between different PUIS and the unfolding trajectory are sparse. To understand such dynamical processes, we study chemical unfolding of a small protein, chicken villin head piece (HP-36), in aqueous dimethyl sulfoxide (DMSO) solution. We carry out molecular dynamics simulations at various solution compositions under ambient conditions.

Protein-Nucleic acid Interactions

Using tertiary structure for the computation of highly accurate multiple RNA alignments with the SARA-Coffee package

Carsten Kemena, Giovanni Bussotti , Emidio Capriotti,Marc A. Marti-Renom and Cedric Notredame[Centre for Genomic Regulation (CRG)]

Bioinformatics. **29**, 1112-1119, 2013.

Aligning RNAs is useful to search for homologous genes, study evolutionary relationships, detect conserved regions and identify any patterns that may be of biological relevance. Poor levels of conservation among homologs, however, make it difficult to compare RNA sequences, even when considering closely evolutionary related sequences. We describe SARA-Coffee, a tertiary structure-based multiple RNA aligner, which has been validated using BRAliDARTS, a new benchmark framework designed for evaluating tertiary structure–based multiple RNA aligners. We provide two methods to measure the capacity of alignments to match corresponding secondary and tertiary structure features.

Network-guided sparse regression modeling for detection of gene-by-gene interactions

Chen Lu [Boston University], Jeanne Latourelle, George T. O'Connor, Josée Dupuis andEric D. Kolaczyk

Bioinformatics. **29**, 1241-1249, 2013.

Genetic variants identified by genome-wide association studies to date explain only a small fraction of total heritability. We propose a novel approach to detect such interactions that uses penalized regression and sparse estimation principles, and incorporates outside biological knowledge through a network-based penalty. We tested our new method on simulated and real data. Simulation showed that with reasonable outside biological knowledge, our method performs noticeably better than stage-wise strategies in finding true interactions, especially when the marginal strength of main effects is weak.

Study of base pair mutations in proline-rich homeodomain (PRH)–DNA complexes using molecular dynamics

Seifollah Jalili [Toosi University of Technology], Leila Karami, Jeremy Schofield

Euro.biophy. jour., **42**, 427-440, 2013.

Proline-rich homeodomain (PRH) is a regulatory protein controlling transcription and gene expression processes by binding to the specific sequence of DNA, especially to the sequence 5′-TAATNN-3′. The impact of base pair mutations on the binding between the PRH protein and DNA is investigated using molecular dynamics and free energy simulations to identify DNA sequences that form stable complexes with PRH. Three 20-ns molecular dynamics simulations (PRH–TAATTG, PRH–TAATTA and PRH–TAATGG complexes) in explicit solvent water were performed to investigate three complexes structurally.

The Effect and Role of Carbon Atoms in Poly(β-amino ester)s for DNA Binding and Gene Delivery

Corey J. Bishop , Tiia-Maaria Ketola , Stephany Y. Tzeng , Joel C. Sunshine , Arto Urtti ,Helge Lemmetyinen , Elina Vuorimaa-Laukkanen ,Marjo Yliperttula , and Jordan J. Green [Johns Hopkins University School of Medicine]

J. Am. Chem. Soc., 2013, **135**, 6951–6957

Polymeric vectors for gene delivery are a promising alternative for clinical applications, as they are generally safer than viral counterparts. Our objective was to further our mechanistic understanding of polymer structure–function relationships to allow the rational design of new biomaterials. Utilizing poly(β-amino ester)s (PBAEs), we investigated polymer–DNA binding by systematically varying the polymer molecular weight, adding single carbons to the backbone and side chain of the monomers that constitute the polymers, and varying the type of polymer end group.

Protein-Nucleic Acid Interactions (Cont'd)

Molecular dynamics study of DNA binding by INT-DBD under a polarized force field

Xue X. Yao, Chang G. Ji [East China Normal University], Dai Q. Xie,John Z.H. Zhang

J. Comp. Chem., **34**, 1136–1142, 2013.

The DNA binding domain of transposon Tn916 integrase (INT-DBD) binds to DNA target site by positioning the face of a three-stranded antiparallel β-sheet within the major groove. As the negatively charged DNA directly interacts with the positively charged residues of INT-DBD, the electrostatic interaction is expected to play an important role in the dynamical stability of the protein–DNA binding complex. In the current work, the combined use of quantum-based polarized protein-specific charge (PPC) for protein and polarized nucleic acid-specific charge (PNC) for DNA were employed in molecular dynamics simulation to study the interaction dynamics between INT-DBD and DNA.

Nucleic Acids

Characterizing the Protonation State of Cytosine in Transient G•C Hoogsteen Base Pairs in Duplex DNA

Evgenia N. Nikolova, Garrett B. Goh, Charles L. Brooks, III, and Hashim M. Al-Hashimi [University of Michigan]

J. Am. Chem. Soc., 2013, **135**, 6766–6769

G•C Hoogsteen base pairs can form transiently in duplex DNA and play important roles in DNA recognition, replication, and repair. G•C Hoogsteen base pairs are thought to be stabilized by protonation of cytosine N3, which affords a second key hydrogen bond, but experimental evidence for this is sparse because the proton cannot be directly visualized by X-ray crystallography and nuclear magnetic resonance spectroscopy. Here, we combine NMR and constant pH molecular dynamics simulations to directly investigate the pKa of cytosine N3 in a chemically trapped N1-methyl-G•C Hoogsteen base pair within duplex DNA.

Toward Improved Description of DNA Backbone: Revisiting Epsilon and Zeta Torsion Force Field Parameters

Marie Zgarbová, F. Javier Luque, Jiří Šponer, Thomas E. Cheatham, III, Michal Otyepka, and Petr Jurečka [Palacky University]

J. Chem. Theor. and Comp, **9**, 2339–2354, 2013.

We present a refinement of the backbone torsion parameters ε and ζ of the Cornell et al. AMBER force field for DNA simulations. The new parameters, denoted as εζOL1, were derived from quantum-mechanical calculations with inclusion of conformation-dependent solvation effects according to the recently reported methodology (J. Chem. Theory Comput.2012, 7(9), 2886–2902). The performance of the refined parameters was analyzed by means of extended molecular dynamics (MD) simulations for several representative systems. The results showed that the εζOL1 refinement improves the backbone description of B-DNA double helices and the G-DNA stem.

Nucleic Acids (Cont'd)

Coarse-Grained Model for Predicting RNA Folding Thermodynamics

Natalia A. Denesyuk and D. Thirumalai [University of Maryland,]

J. Phys. Chem. B., **117**, 4901–49119, 2013**.**

We present a thermodynamically robust coarse-grained model to simulate folding of RNA in monovalent salt solutions. The model includes stacking, hydrogen bond, and electrostatic interactions as fundamental components in describing the stability of RNA structures. The stacking interactions are parametrized using a set of nucleotide-specific parameters, which were calibrated against the thermodynamic measurements for single-base stacks and base-pair stacks. All hydrogen bonds are assumed to have the same strength, regardless of their context in the RNA structure.

Structures, Dynamics, and Stabilities of Fully Modified Locked Nucleic Acid (β-d-LNA and α-l-LNA) Duplexes in Comparison to Pure DNA and RNA Duplexes

Gorle Suresh and U. Deva Priyakumar [International Institute of Information Technology, Hyderabad]

J. Phys. Chem. B., **117**, 5556–5564, 2013**.**

A!

Locked nucleic acid (LNA) is a chemical modification which introduces a −O–CH2– linkage in the furanose sugar of nucleic acids and blocks its conformation in a particular state. Two types of modifications, namely, 2′-O,4′-C-methylene-β-D-ribofuranose (β-D-LNA) and 2′-O,4′-C-methylene-α-L-ribofuranose (α-L-LNA), have been shown to yield RNA and DNA duplex-like structures, respectively. LNA modifications lead to increased melting temperatures of DNA and RNA duplexes, and have been suggested as potential therapeutic agents in antisense therapy. In this study, molecular dynamics (MD) simulations were performed on fully modified LNA duplexes and pure DNA and RNA duplexes sharing a similar sequence to investigate their structure, stabilities, and solvation properties.

Surfaces, Catalysts, and Materials Subjects

Nonrandom adsorption of polyelectrolyte chains on finite regularly charged surfaces

Sandra C. C. Nunes, P. Pinto, A. A. C. C. Pais [University of Coimbra]

J. Comp. Chem., **34**, 1198–1209, 2013.

Adsorption phenomena are relevant in a wide variety of subjects, from biophysics to technological applications. Different aspects, such as molecular recognition, multilayer deposition, and dynamics of polymer adsorption have been addressed. The methodologies used range from analytical and numerical methods to molecular dynamics or Monte Carlo simulations. In this work, a coarse-grained model is used to explore the adsorption of charged backbones to oppositely charged regions of a surface.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Some case studies on application of "rm^2" metrics for judging quality of quantitative structure–activity relationship predictions: Emphasis on scaling of response data

Kunal Roy [Jadavpur University], Pratim Chakraborty, Indrani Mitra, Probir Kumar Ojha, Supratik Kar,Rudra Narayan Das

J. Comp. Chem., **34**, 1071–1082, 2013.

Quantitative structure–activity relationship (QSAR) techniques have found wide application in the fields of drug design, property modeling, and toxicity prediction of untested chemicals. A rigorous validation of the developed models plays the key role for their successful application in prediction for new compounds. The rm^2 metrics introduced by Roy et al. have been extensively used by different research groups for validation of regression-based QSAR models. This concept has been further advanced here with introduction of scaling of response data prior to computation of rm^2.

Quantitative Structure–Activity Relationship Models for Ready Biodegradability of Chemicals

Kamel Mansouri , Tine Ringsted , Davide Ballabio[University of Milano Bicocca] ,Roberto Todeschini , and Viviana Consonni

J.Chem. Infor. and Mod. **53**, 867–878, 2013.

S!

The European REACH regulation requires information on ready biodegradation, which is a screening test to assess the biodegradability of chemicals. At the same time REACH encourages the use of alternatives to animal testing which includes predictions from quantitative structure–activity relationship (QSAR) models. The aim of this study was to build QSAR models to predict ready biodegradation of chemicals by using different modeling methods and types of molecular descriptors. Particular attention was given to data screening and validation procedures in order to build predictive models.

Quantitative Structure–Activity Relationship Models of Clinical Pharmacokinetics: Clearance and Volume of Distribution

Vijay K. Gombar [Lilly Corporate Center, Indianapolis]and Stephen D. Hall

J.Chem. Infor. and Mod. **53**, 948–957, 2013.

Reliable prediction of two fundamental human pharmacokinetic (PK) parameters, systemic clearance (CL) and apparent volume of distribution (Vd), determine the size and frequency of drug dosing and are at the heart of drug discovery and development. Traditionally, estimated CL and Vd are derived from preclinical in vitro and in vivo absorption, distribution, metabolism, and excretion (ADME) measurements. In this paper, we report quantitative structure–activity relationship (QSAR) models for prediction of systemic CL and steady-state Vd (Vdss) from intravenous (iv) dosing in humans.

Potentials and Parameters

Parameter Importance in FRAP Acquisition and Analysis: A Simulation Approach

Juliane Mai [Helmholtz Centre for Environmental Research],Saskia Trump, Irina Lehmann, Sabine Attinger,

Biophysical Journal. **104**, 2089–2097, 2013.

Fluorescence recovery after photobleaching (FRAP) is a widespread technique used to determine intracellular reaction and diffusion parameters. In recent years, due to technical advances and an increasing number of mathematical models for analysis, there was a resurging interest in FRAP applications. We study potential influences on FRAP acquisition and analysis like initial fluorescence distribution, membrane passage, and geometrical aspects. Monte Carlo simulations are employed for the investigation of reaction-diffusion processes to additionally include cases in which no analytical description is available.

Parameterization of a reactive force field using a monte carlo algorithm

E. Iype, M. Hütter, A. P. J. Jansen, S. V. Nedea, C. C. M. Rind[Eindhoven University of Technology]

J. Comp. Chem., **34**, 1143–1154, 2013.

Parameterization of a molecular dynamics force field is essential in realistically modeling the physicochemical processes involved in a molecular system. This step is often challenging when the equations involved in describing the force field are complicated as well as when the parameters are mostly empirical. ReaxFF is one such reactive force field which uses hundreds of parameters to describe the interactions between atoms. The optimization of the parameters in ReaxFF is done such that the properties predicted by ReaxFF matches with a set of quantum chemical or experimental data.

Polarizable simulations with second order interaction model (POSSIM) force field: Developing parameters for protein side-chain analogues

Xinbi Li, Sergei Y. Ponomarev, Qina Sa,Daniel L. Sigalovsky, George A. Kaminski[Worcester Polytechnic Institute]

J. Comp. Chem., **34**, 1241–1250, 2013.

A previously introduced polarizable simulations with second-order interaction model (POSSIM) force field has been extended to include parameters for small molecules serving as models for peptide and protein side-chains. Parameters have been fitted to permit reproducing many-body energies, and geometries and liquid-phase heats of vaporization and densities. Quantum mechanical and experimental data have been used as the target for the fitting. The POSSIM framework combines accuracy of a polarizable force field and computational efficiency of the second-order approximation of the full-scale induced point dipole polarization formalism.

Molecular Dynamics

Molecular Energetics in the Capsomere of Virus-Like Particle Revealed by Molecular Dynamics Simulations

Lin Zhang, Ronghong Tang, Shu Bai, Natalie K. Connors, Linda H. L. Lua, Yap P. Chuan, Anton P. J. Middelberg, and Yan Sun [Tianjin University]

J. Phys. Chem. B., **117**, 5411–5421, 2013**.**

Virus-like particles (VLPs) are highly organized nanoparticles that have great potential in vaccinology, gene therapy, drug delivery, and materials science. However, the application of VLPs is hindered by obstacles in their design and production due to low efficiency of self-assembly. In the present study, all-atom (AA) MD simulations coupled with the molecular mechanics-Poisson–Boltzmann surface area (MM-PBSA) method are utilized to examine the molecular interactions in the capsomere of a murine polyomavirus (MPV) VLP.

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Molecular Dynamics (Cont'd)

Scoring Multipole Electrostatics in Condensed-Phase Atomistic Simulations

Tristan Bereau, Christian Kramer, Fabien W. Monnard, Elisa S. Nogueira, Thomas R. Ward, and Markus Meuwly [University of Basel,]

J. Phys. Chem. B., **117**, 5460–5471, 2013**.**

A!

Permanent multipoles (MTPs) embody a natural extension to common point-charge (PC) representations in atomistic simulations. In this work, we propose an alternative to the computationally expensive MTP molecular dynamics simulations by running a simple PC simulation and later reevaluate—"score''—all energies using the more detailed MTP force field. The method, which relies on the assumption that the PC and MTP force fields generate closely related phase spaces, is accomplished by enforcing identical sets of monopoles between the two force fields—effectively highlighting the higher MTP terms as a correction to the PC approximation.

Molecular Principle of Topotecan Resistance by Topoisomerase I Mutations through Molecular Modeling Approaches

Peichen Pan, Youyong Li, Huidong Yu, Huiyong Sun, and Tingjun Hou [Zhejiang University]

J.Chem. Infor. and Mod. **53**, 997–1006, 2013.

Originally isolated from natural products, camptothecin (CPT) has provided extensive playing fields for the development of antitumor drugs. Two of the most successful analogs of CPT, topotecan and irinotecan, have been approved by the FDA for the treatment of colon cancer and ovarian cancer, as well as other cancers. In this study, a series of computational approaches from molecular dynamics (MD) simulations to steered molecular dynamics (SMD) simulations and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) binding free energy calculations were employed to uncover the molecular principle of the topotecan resistance induced by three mutations in DNA topoisomerase I, including E418K, G503S, and D533G.

How calcium inhibits the magnesium-dependent kinase gsk3β: A molecular simulation study

Shao-Yong Lu,Zhi-Min Huang,Wen-Kang Huang,Xin-Yi Liu1,Ying-Yi Chen,Ting Shi, Jian Zhang [Shanghai JiaoTong University]

Proteins: Stru. Fun. & Bioinf., **81**, 740–753, 2013.

Glycogen synthase kinase 3β (GSK3β) is a ubiquitous serine/threonine kinase that plays a pivotal role in many biological processes. GSK3β catalyzes the transfer of γ-phosphate of ATP to the unique substrate Ser/Thr residues with the assistance of two natural activating cofactors Mg2+. Interestingly, the biological observation reveals that a non-native Ca2+ ion can inhibit the GSK3β catalytic activity. Here, the inhibitory mechanism of GSK3β by the displacement of native Mg2+ at site 1 by Ca2+ was investigated by means of 80 ns comparative molecular dynamics (MD) simulations of the GSK3β•••Mg2+-2/ATP/ Mg2+-1 and GSK3β•••Mg2+-2/ATP/Ca2+-1 systems.

QM and QM/MM

Understanding the electronic energy transfer pathways in the trimeric and hexameric aggregation state of cyanobacteria phycocyanin within the framework of förster theory

Yanliang Ren, Bo Chi, Osama Melhem, Ke Wei, Lingling Feng,Yongjian Li, Xinya Han, Ding Li, Ying Zhang, Jian Wan, Xin Xu [Central China Normal University], Minghui Yang

J. Comp. Chem., **34**, 1005–1012, 2013.

In the present study, the electronic energy transfer pathways in trimeric and hexameric aggregation state of cyanobacteria C-phycocyanin (C-PC) were investigated in term of the Förster theory. The corresponding excited states and transition dipole moments of phycocyanobilins (PCBs) located into C-PC were examined by model chemistry in gas phase at time-dependent density functional theory (TDDFT), configuration interaction-singles (CIS), and Zerner's intermediate neglect of differential overlap (ZINDO) levels, respectively.

Effective fragment potential method in Q-CHEM: A guide for users and developers

Debashree Ghosh, Dmytro Kosenkov, Vitalii Vanovschi, Joanna Flick , Ilya Kaliman , Yihan Shao, Andrew T.B. Gilbert , Anna I. Krylov [University of Southern California] , Lyudmila V. Slipchenko

J. Comp. Chem., **34**, 1060–1070, 2013.

A detailed description of the implementation of the effective fragment potential (EFP) method in the Q-CHEM electronic structure package is presented. The Q-CHEM implementation interfaces EFP with standard quantum mechanical (QM) methods such as Hartree–Fock, density functional theory, perturbation theory, and coupled-cluster methods, as well as with methods for electronically excited and open-shell species, for example, configuration interaction, time-dependent density functional theory, and equation-of-motion coupled-cluster models.

QMX: A versatile environment for hybrid calculations applied to the grafting of $Al_2Cl_3Me_3$ on a silica surface

Torsten Kerber[Université Lyon 1], Rachel Nathaniel Kerber,Xavier Rozanska, Philippe Sautet, Paul Fleurat-Lessard

J. Comp. Chem., **34**, 1155–1163, 2013.

We present a new software to easily perform QM:MM and QM:QM' calculations called QMX. It follows the subtraction scheme and it is implemented in the Atomic Simulation Environment (ASE). Special attention is paid to couple molecular calculations with periodic boundaries approaches. QMX inherits the flexibility and versatility of the ASE package: any combination of methods namely force field, semiempirical, first principle, and *ab initio*, can be used as hybrid potential energy surface (PES). Its ease of use is demonstrated by considering the adsorption of $Al_2Cl_3Me_3$ on silica surface and by combining different levels of theory (from standard DFT to MP2 calculations) for the so-called High Level cluster with standard PW91 density functional theory calculations for the Low Level environment.

Energy Flow in the Cryptophyte PE545 Antenna Is Directed by Bilin Pigment Conformation

Carles Curutchet [Universitat de Barcelona], Vladimir I. Novoderezhkin, Jacob Kongsted, Aurora Muñoz-Losa, Rienk van Grondelle, Gregory D. Scholes, and Benedetta Mennucci

J. Phys. Chem. B., **117**, 4263–4273, 2013**.**

Structure-based calculations are combined with quantitative modeling of spectra and energy transfer dynamics to detemine the energy transfer scheme of the PE545 principal light-harvesting antenna of the cryptomonad Rhodomonas CS24. We use a recently developed QM/MM method that allows us to account for pigment–protein interactions at atomic detail in site energies, transition dipole moments, and electronic couplings. In addition, conformational flexibility of the pigment–protein complex is accounted for through MD simulations.

QM and QM/MM (Cont'd)

A QM/MM Study of the Absorption Spectrum of Harmane in Water Solution and Interacting with DNA: The Crucial Role of Dynamic Effects

Thibaud Etienne, Thibaut Very, Eric A. Perpète, Antonio Monari [Université de Lorraine – Nancy], and Xavier Assfeld

J. Phys. Chem. B., **117**, 4973–4980, 2013**.**

We present a time-dependent density functional theory computation of the absorption spectra of one β-carboline system: the harmane molecule in its neutral and cationic forms. The spectra are computed in aqueous solution. The interaction of cationic harmane with DNA is also studied. In particular, the use of hybrid quantum mechanics/molecular mechanics methods is discussed, together with its coupling to a molecular dynamics strategy to take into account dynamic effects of the environment and the vibrational degrees of freedom of the chromophore.

Comparative or Homology Modeling

Influence of Site-Dependent Pigment–Protein Interactions on Excitation Energy Transfer in Photosynthetic Light Harvesting

Eva Rivera, Daniel Montemayor, Marco Masia, and David F. Coker [Boston University]

J. Phys. Chem. B., **117**, 5510–5521, 2013**.**

A site-dependent spectral density system–bath model of the Fenna–Matthews–Olsen (FMO) pigment–protein complex is developed using results from ground-state molecular mechanics simulations together with a partial charge difference model for how the long-range contributions to the chromophore excitation energies fluctuate with environmental configuration. A discussion of how best to consistently process the chromophore excitation energy fluctuation correlation functions calculated in these classical simulations to obtain reliable site-dependent spectral densities is presented.

Critical analysis of the successes and failures of homology models of G protein-coupled receptors

Supriyo Bhattacharya, Alfonso Ramon Lam, Hubert Li, Gouthaman Balaraman, Michiel Jacobus Maria Niesen and Nagarajan Vaidehi[Beckman Research Institute of the City of Hope, Duarte]

Proteins: Stru. Fun. & Bioinf., **81**, 729–739, 2013.

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We present a critical assessment of the performance of our homology model refinement method for G protein-coupled receptors (GPCRs), called LITICon that led to top ranking structures in a recent structure prediction assessment GPCRDOCK2010. GPCRs form the largest class of drug targets for which only a few crystal structures are currently available. Therefore, accurate homology models are essential for drug design in these receptors. We submitted five models each for human chemokine CXCR4 (bound to small molecule IT1t and peptide CVX15) and dopamine D3DR (bound to small molecule eticlopride) before the crystal structures were published.

Comparative / Homology Modeling (Cont'd)

Coarse- and fine-grained models for proteins: Evaluation by decoy discrimination

Chris Kauffman [George Mason University], George Karypis

Proteins: Stru. Fun. & Bioinf., **81**, 754–773, 2013.

Coarse-grained models for protein structure are increasingly used in simulations and structural bioinformatics. In this study, we evaluated the effectiveness of three granularities of protein representation based on their ability to discriminate between correctly folded native structures and incorrectly folded decoy structures. The three levels of representation used one bead per amino acid (coarse), two beads per amino acid (medium), and all atoms (fine). Multiple structure features were compared at each representation level including two-body interactions, three-body interactions, solvent exposure, contact numbers, and angle bending.

Ligand Docking

Systematic and efficient side chain optimization for molecular docking using a cheapest-path procedure

Marcel Schumann [Thomas Jefferson University], Roger S. Armen

J. Comp. Chem., **34**, 1258–1269, 2013.

Molecular docking of small-molecules is an important procedure for computer-aided drug design. Modeling receptor side chain flexibility is often important or even crucial, as it allows the receptor to adopt new conformations as induced by ligand binding. However, the accurate and efficient incorporation of receptor side chain flexibility has proven to be a challenge due to the huge computational complexity required to adequately address this problem. Here we describe a new docking approach with a very fast, graph-based optimization algorithm for assignment of the near-optimal set of residue rotamers.

Automated Ligand- and Structure-Based Protocol for in Silico Prediction of Human Serum Albumin Binding

Michelle Lynn Hall, William L. Jorgensen, and Lewis Whitehead [Novartis Institutes for Biomedical Research]

J.Chem. Infor. and Mod. **53**, 907–922, 2013.

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Plasma protein binding has a profound impact on the pharmacokinetic and pharmacodynamic properties of many drug candidates and is thus an integral component of drug discovery. Nevertheless, extant methods to examine small-molecule interactions with plasma protein have various limitations, thus creating a need for alternative methods. Herein we present a comprehensive and cross-validated in silico workflow for the prediction of small-molecule binding to Human Serum Albumin (HSA), the most ubiquitous plasma protein.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 43, 2013.

1–10 **A conceptual basis to encode and detect organic functional groups in XML,** Punnaivanam Sankar[Pondicherry Engineering College] , Alain Krief , Durairaj Vijayasarathi

A conceptual basis to define and detect organic functional groups is developed. The basic model of a functional group is termed as a primary functional group and is characterized by a group center composed of one or more group center atoms bonded to terminal atoms and skeletal carbon atoms.

11–20 **The derivation of a chiral substituent code for secondary alcohols and its application to the prediction of enantioselectivity,** Jing-Jie Suoa, Qing-You Zhanga [Henan University], Jing-Ya Lia, Yan-Mei Zhoua, Lu Xub

A chiral substituent code was proposed based on the features of secondary alcohols, in which a chiral center is attached to two substituents in addition to OH and H substituents. The new chirality code, which was generated by predefining positional information of four substituents attached to stereocenter, was applied to two datasets composed of secondary alcohols as the enantioselective products of asymmetric reactions.

21–30 **Insight into structural and biochemical determinants of substrate specificity of PFI1625c: Correlation analysis of protein-peptide molecular models,** Kimjolly Lhouvuma, Vibin Ramakrishnanb, Vishal Trivedia [Indian Institute of Technology-Guwahati]

See Applications / Protein-Protein Interactions.

31–40 **Effects of amine organic groups as lattice in ZSM-5 on the hydrolysis of dimethyl ether,** Jittima Meepraserta, Siriporn Jungsuttiwongb, Thanh N. Truongc, Supawadee Namuangruka,[Technology Development Agency, Klong Luang]

See Applications / Zeolites.

41–46 **3D shape-based analysis of cell line-specific compound response in cancers,** Ningning He, Xiaoqi Wang, Nayoung Kim, Jong-Seok Lim, Sukjoon Yoon[Sookmyung Women's University],

See Applications / Medicinal Chemmistry and Drug Design.

Journal of Computational Chemistry, 134, (12), 2013.

987–1004 **Electronic structure of the S_1 state in methylcobalamin: Insight from CASSCF/MC-XQDPT2, EOM-CCSD, and TD-DFT calculations,** Karina Kornobis, Neeraj Kumar, Piotr Lodowski, Maria Jaworska, Piotr Piecuch [University of Louisville], Jesse J. Lutz, Bryan M. Wong, Pawel M. Kozlowski

The methylcobalamin cofactor (MeCbl), which is one of the biologically active forms of vitamin B_{12}, has been the subject of many spectroscopic and theoretical investigations. Traditionally, the lowest-energy part of the photoabsorption spectrum of MeCbl (the so-called α/β band) has been interpreted as an $S_0 \rightarrow S_1$ electronic transition dominated by $\pi \rightarrow \pi^*$ excitations associated with the C=C stretching of the corrin ring. To resolve the existing controversy about the interpretation of the S_1 state of MeCbl, calculations have been performed using two independent *ab initio* wavefunction-based methods.

1005–1012 **Understanding the electronic energy transfer pathways in the trimeric and hexameric aggregation state of cyanobacteria phycocyanin within the framework of förster theory,** Yanliang Ren, Bo Chi, Osama Melhem, Ke Wei, Lingling Feng,Yongjian Li, Xinya Han, Ding Li, Ying Zhang, Jian Wan, Xin Xu [Central China Normal University], Minghui Yang

See Methodology / QM and QM/MM.

1013–1023 **NMR shielding constants of CuX, AgX, and AuX (X = F, Cl, Br, and I) investigated by density functional theory based on the douglas–kroll–hess Hamiltonian,** Terutaka Yoshizawa, Shigeyoshi Sakaki[Kyoto University]

Two-component relativistic density functional theory (DFT) with the second-order Douglas–Kroll–Hess (DKH2) one-electron Hamiltonian was applied to the calculation of nuclear magnetic resonance (NMR) shielding constant.

1024–1034 **Comparison of thermodynamic integration and Bennett's acceptance ratio for calculating relative protein-ligand binding free energies,** Anita de Ruiter, Stefan Boresch, Chris Oostenbrink[BOKU – University of Natural Resources and Life Sciences, Muthgasse]

See Applications / Free Energy Calculations**.**

1035–1045 **Bis-μ-oxo and μ-η^2:η^2-peroxo dicopper complexes studied within (time-dependent) density-functional and many-body perturbation theory,** M. Rohrmüller[Universität Paderborn] ,S. Herres-Pawlis , M. Witte ,W. G. Schmidt

Based on the equilibrium geometries of $[Cu_2(dbdmed)_2O_2]^{2+}$ and $[Cu_2(en)_2O_2]^{2+}$ obtained within density-functional theory, we investigate their molecular electronic structure and optical response.

1046–1059 **PDECO: Parallel differential evolution for clusters optimization,** Zhanghui Chen, Xiangwei Jiang, Jingbo Li [Chinese Academy of Sciences], Shushen Li, Linwang Wang

The optimization of the atomic and molecular clusters with a large number of atoms is a very challenging topic. This article proposes a parallel differential evolution (DE) optimization scheme for large-scale clusters.

It combines a modified DE algorithm with improved genetic operators and a parallel strategy with a migration operator to address the problems of numerous local optima and large computational demanding.

1060–1070 **Effective fragment potential method in Q-CHEM: A guide for users and developers,** Debashree Ghosh , Dmytro Kosenkov , Vitalii Vanovschi , Joanna Flick , Ilya Kaliman , Yihan Shao, Andrew T.B. Gilbert , Anna I. Krylov [University of Southern California] , Lyudmila V. Slipchenko

See Methodology / QM and QM/MM.

1071–1082 **Some case studies on application of "rm^2" metrics for judging quality of quantitative structure–activity relationship predictions: Emphasis on scaling of response data,** Kunal Roy [Jadavpur University], Pratim Chakraborty, Indrani Mitra, Probir Kumar Ojha, Supratik Kar,Rudra Narayan Das

See Methodology / QSAR.

Journal of Computational Chemistry, 134, (13), 2013.

1083–1093 **Monte carlo configuration interaction applied to multipole moments, ionisation energies and electron affinities,** Jeremy P. Coe, Daniel J. Taylor, Martin J. Paterson[Heriot-Watt University]

The method of Monte Carlo configuration interaction (MCCI) (Greer, J. Chem. Phys. 1995a, 103, 1821; Tong, Nolan, Cheng, and Greer, Comp. Phys. Comm. 2000, 142, 132) is applied to the calculation of multipole moments. We look at the ground and excited state dipole moments in carbon monoxide.

1094–1100 **Theoretical study of ionization and one-electron oxidation potentials of *N*-heterocyclic compounds,** Liudmyla K. Sviatenko, Leonid Gorb,Frances C. Hill, Jerzy Leszczynski[Jackson State University]

A number of density functionals was utilized to predict gas-phase adiabatic ionization potentials (IPs) for nitrogen-rich heterocyclic compounds. We developed generally applicable protocols that could successfully predict the gas-phase adiabatic ionization potentials of nitrogen-rich heterocyclic compounds and their standard oxidation potentials in AN.

1101–1111 **First principles study of gallium cleaning for hydrogen-contaminated α-Al_2O_3(0001) surfaces,** Rui Yang, [the Australian National University] Alistair P. Rendell

The use of gallium for cleaning hydrogen-contaminated Al_2O_3 surfaces is explored by performing first principles density functional calculations of gallium adsorption on a hydrogen-contaminated Al-terminated α-Al_2O_3(0001) surface.

1112–1124 **A multiscale coarse-grained polarizable solvent model for handling long tail bulk electrostatics,** Michel Masella [Institut de biologie et de technologies de Saclay], Daniel Borgis,Philippe Cuniasse

A multiscale coarse-grained approach able to handle efficiently the solvation of microscopic solutes in extended chemical environment is described. That approach is able to compute readily and efficiently very

long-range solute/solvent electrostatic microscopic interactions, up to the 1-μm scale, by considering a reduced amount of computational resources.

1125–1135 **Could an anisotropic molecular mechanics/dynamics potential account for sigma hole effects in the complexes of halogenated compounds?,** Krystel El Hage, Jean-Philip Piquemal,Zeina Hobaika, Richard G. Maroun,Nohad Gresh [Laboratoire de Chimie Biochimie Pharmacologiques et Toxicologiques]

Halogenated compounds are gaining an increasing importance in medicinal chemistry and materials science. Ab initio quantum chemistry (QC) has unraveled the existence of a "sigma hole" along the C—X (X = F, Cl, Br, I) bond, namely, a depletion of electronic density prolonging the bond, concomitant with a build-up on its sides, both of which are enhanced along the F < Cl < Br < I series. We have evaluated whether these features were intrinsically built-in in an anisotropic, polarizable molecular mechanics (APMM) procedure such as SIBFA.

1136–1142 **Molecular dynamics study of DNA binding by INT-DBD under a polarized force field,** Xue X. Yao, Chang G. Ji [East China Normal University], Dai Q. Xie,John Z.H. Zhang

See Applications / Protein-Nucleic acids.

1143–1154 **Parameterization of a reactive force field using a monte carlo algorithm,** E. Iype, M. Hütter, A. P. J. Jansen, S. V. Nedea, C. C. M. Rind[Eindhoven University of Technology]

See Methodology / Potentilas and Parameters.

1155–1163 **QMX: A versatile environment for hybrid calculations applied to the grafting of $Al_2Cl_3Me_3$ on a silica surface,** Torsten Kerber[Université Lyon 1], Rachel Nathaniel Kerber,Xavier Rozanska, Philippe Sautet, Paul Fleurat-Lessard

See Methodology / QM and QM/MM.

1164–1175 **PHI: A powerful new program for the analysis of anisotropic monomeric and exchange-coupled polynuclear d- and f-block complexes**[†], Nicholas F [Monash University]. Chilton, Russell P. Anderson, Lincoln D. Turner,Alessandro Soncini, Keith S. Murray*

A new program, *PHI*, with the ability to calculate the magnetic properties of large spin systems and complex orbitally degenerate systems, such as clusters of d-block and f-block ions, is presented. The program can intuitively fit experimental data from multiple sources, such as magnetic and spectroscopic data, simultaneously.

1177–1188 **Grand challenges in quantum-classical modeling of molecule–surface interactions,** Claudia R. Herbers, Chunli Li, Nico F. A. van der Vegt[Technische Universität Darmstadt]

A detailed understanding of the adsorption of small molecules or macromolecules to a materials surface is of importance, for example, in the context of material and biomaterial research. Classical atomistic simulations in principle provide microscopic insight in the complex entropic and enthalpic interplay at the interface. We will discuss in this review the current state-of-the-art of quantum-classical modeling of molecule–surface interactions and outline the major challenges in this field.

Journal of Computational Chemistry, 134, (14), 2013.

1189–1197 **Exact ligand cone angles,** Jenna A. Bilbrey, Arianna H. Kazez,Jason Locklin, Wesley D. Allen[University of Georgia]

Many properties of transition-metal complexes depend on the steric bulk of bound ligands, usually quantified by the Tolman (θ) and solid (θ) cone angles, which have proven utility but suffer from various limitations and coarse approximations. Here, we present an improved, mathematically rigorous method to determine an exact cone angle (θ°) by solving for the most acute right circular cone that contains the entire ligand.

1198–1209 **Nonrandom adsorption of polyelectrolyte chains on finite regularly charged surfaces,** Sandra C. C. Nunes, P. Pinto, A. A. C. C. Pais[University of Coimbra]

See Surfaces, Catalysts and Materials.

1210–1217 **The adaptive hierarchical expansion of the kinetic energy operator,** Daniel Strobusch, Mathias Nest,Christoph Scheurer[Technische Universität München]

The hierarchical expansion of the kinetic energy (HEKE) operator in curvilinear coordinates presented recently (Strobusch and Scheurer, J. Chem. Phys. 2011a, 135, 124102; Strobusch and Scheurer, J. Chem. Phys. 2011b, 135, 144101) relies on a many-body expansion of the metric tensor. It is shown how this expansion can be adapted to a specific system.

1218–1225 **Linearity condition for orbital energies in density functional theory (III): Benchmark of total energies,** Yutaka Imamura, Rie Kobayashi,Hiromi Nakai[Waseda University]

This study presents a numerical assessment of total energy related physical quantities estimated using the orbital-specific (OS) global and range-separated hybrid functionals, designed to satisfy the linearity condition for orbital energies (LCOE).

1226–1240 **Grid-based molecular footprint comparison method for docking and *de novo* design: Application to HIVgp41,** Trent E. Balius, William J. Allen,Sudipto Mukherjee ,Robert C. Rizzo

See Applications / Medicinal Chemmistry and Drug Design.

1241–1250 **Polarizable simulations with second order interaction model (POSSIM) force field: Developing parameters for protein side-chain analogues,** Xinbi Li, Sergei Y. Ponomarev, Qina Sa,Daniel L. Sigalovsky, George A. Kaminski[Worcester Polytechnic Institute]

See Methodology / Potentilas and Parameters.

1251–1257 **Protein-specific force field derived from the fragment molecular orbital method can improve protein–ligand binding interactions,** Le Chang, Takeshi Ishikawa, Kazuo Kuwata, Shoji Takada[Kyoto University]

See Applications / Membrane proteins and Lipid peptide interactions.

1258–1269 **Systematic and efficient side chain optimization for molecular docking using a cheapest-path procedure,** Marcel Schumann [Thomas Jefferson University], Roger S. Armen

See Methodology / Ligand Docking.

Journal of Molecular Modeling, 19 (5), May, 2013.

1945-1952 **Theoretical study of the pH-dependent antioxidant properties of vitamin C,** Jon I. Mujika, Jon M. Matxain[Euskal Herriko Unibertsitatea (UPV/EHU)]

Molecules acting as antioxidants capable of scavenging reactive oxygen species (ROS) are of utmost importance in the living cell. Vitamin C is known to be one of these molecules. In this study we have analyzed the reactivity of vitamin C toward the ·*OH* and ·*OOH* ROS species, in all acidic, neutral and basic media.

1953-1958 **Heavy periodane,** Jon M. Azpiroz, Diego Moreno, Alonso Ramirez-Manzanares, Jesus M. Ugalde, Miguel Angel Mendez-Rojas, Gabriel Merino[Centro de Investigación y de Estudios Avanzados]

The potential energy surface of the hypothetical NaMgAlSiPSCl system (heavy periodane) is exhaustively analyzed via the gradient embedded genetic algorithm (GEGA) in combination with density functional theory (DFT) computations.

1959-1965 **Dissociation quenching using exceptional points,** R. Lefebvre [Université Paris-Sud], O. Atabek

We examine a short way to reach an exceptional point that corresponds to a coalescence of two resonance energies. The application concerns the photodissociation of the Na_2 molecule exposed to a laser field. In this case, the resonances can be correlated with the field-free vibrational states of the diatomic species.

1967-1972 **Computational study of Be_2 using Piris natural orbital functional,** Jon M. Matxain [University of the Basque Country (UPV/EHU)], Fernando Ruipérez, Mario Piris

The third (PNOF3), fourth (PNOF4) and fifth (PNOF5) versions of the Piris natural orbital functional were used to characterize the beryllium dimer. The results obtained were compared to those gained afforded by CASSCF and CASPT2 as well as experimental data.

1973-1979 **Theoretical study on electronic spectra and interaction in $[Au_3]$-L-$[Au_3]$ (L = C_6F_6,Ag^+) complexes,** Fernando Mendizabal[Universidad de Chile], Richard Salazar

The electronic structure and spectroscopic properties of $[Au_3(\mu\text{-}C(OEt) = NC_6H_4CH_3)_3]_n$-$(C_6F_6)_m$ and $[Au_3(\mu\text{-}C^2,N^3\text{-bzim})_3]_n$-$(Ag^+)_m$ were studied at the B3LYP, PBE and TPSS levels. The interaction between the $[Au_3]$ cluster and L (C_6F_6, Ag^+) was analyzed.

1981-1984 **Role of gold in a complex cascade reaction involving two electrocyclization steps,** Jason G. Harrison, Dean J. Tantillo[University of California–Davis]

The electronic structure and spectroscopic properties of $[Au_3(\mu\text{-}C(OEt) = NC_6H_4CH_3)_3]_n\text{-}(C_6F_6)_m$ and $[Au_3(\mu\text{-}C^2,N^3\text{-bzim})_3]_n\text{-}(Ag^+)_m$ were studied at the B3LYP, PBE and TPSS levels. The interaction between the $[Au_3]$ cluster and L (C_6F_6, Ag^+) was analyzed.

1985-1994 **Effect of stepwise microhydration on the methylammonium···phenol and ammonium···phenol interaction,** Ana A. Rodríguez-Sanz, J. Carrazana-García, Enrique M. Cabaleiro-Lago [Universidade de Santiago de Compostela], Jesús Rodríguez-Otero

A computational study has been performed for studying the characteristics of the interaction of phenol with ammonium and methylammonium cations. The effect of the presence of water molecules has also been considered by microhydrating the clusters with up to three water molecules.

1995-2005 **Structural, mechanical and electronic properties of *nano-fibriform* silica and its organic functionalization by dimethyl silane: a SCC-DFTB approach,** Maurício Chagas da Silva, Egon Campos dos Santos, Maicon Pierre Lourenço, Hélio Anderson Duarte[Universidade Federal de Minas Gerais]

Self-consistent-charge density-functional tight-binding (SCC-DFTB) approximated method was employed to investigate the structural, mechanical and electronic properties of the zigzag and armchair *nano-fibriform* silica (SNTs) and their outer surface organic modified derivatives (MSNTs) with internal radii in the range of 8 to 36 Å.

2007-2014 **Three–dimensional effective mass Schrödinger equation: harmonic and Morse-type potential solutions,** G. Ovando[Universidad Autónoma Metropolitana—Azcapotzalco], J. Morales, J. L. López-Bonilla

In this work, a scheme to generate exact wave functions and eigenvalues for the spherically symmetric three-dimensional position-dependent effective mass Schrödinger equation is presented.

2015-2026 C**omparative theoretical study of the UV/Vis absorption spectra of styrylpyridine compounds using TD-DFT calculations,** Maria Eugenia Castro, M. Judith Percino, Victor M. Chapela, Guillermo Soriano-Moro, Margarita Ceron, Francisco J. Melendez[Ciudad Universitaria, Col. San Manuel]

This study examined absorption properties of 2-styrylpyridine, *trans*-2-(*m*-cyanostyryl)pyridine,*trans*-2-[3-methyl-(*m*-cyanostyryl)]pyridine, and *trans*-4-(*m*-cyanostyryl)pyridine compounds based on theoretical UV/Vis spectra, with comparisons between time-dependent density functional theory (TD-DFT) using B3LYP, PBE0, and LC-ωPBE functionals.

2027-2033 **Transition energy and potential energy curves for ionized inner-shell states of CO, O_2 and N_2 calculated by several inner-shell multiconfigurational approaches,** Carlos E. V. de Moura, Ricardo R. Oliveira, Alexandre B. Rocha[Cidade Universitária]

Potential energy curves and inner-shell ionization energies of carbon monoxide, oxygen and nitrogen molecules were calculated using several forms of the inner-shell multiconfigurational self-consistent field (IS-MCSCF) method—a recently proposed protocol to obtain specifically converged inner-shell states at this level.

2091-2095 **Simulation of laser radiation effects on low dimensionality structures,** Iliana María Ramírez [Institución Universitaria], Jorge Iván Usma, Francisco Eugenio López

This paper presents a study on a system comprised of a low-dimensional structure ($Ga_{1-x}Al_xAs$ and GaAs quantum well wire), an intense laser field and an applied magnetic field in axial direction, resulting in a modified structure by interaction with the laser field. A variation of the concentration of aluminum is considered.

2097-2106 **Is the decrease of the total electron energy density a covalence indicator in hydrogen and halogen bonds?,** Emilio L. Angelina, Darío J. R. Duarte, Nélida M. Peruchena[Universidad Nacional del Nordeste]

In this work, halogen bonding (XB) and hydrogen bonding (HB) complexes were studied with the aim of analyzing the variation of the total electronic energy density $H(r_b)$ with the interaction strengthening. The calculations were performed at the MP2/6−311++G(2d,2p) level of approximation.

2107-2118 **Ethylene dimerization catalyzed by mixed phosphine–iminophosphorane nickel(II) complexes: a DFT investigation,** Vincent Tognetti, Antoine Buchard, Audrey Auffrant, Ilaria Ciofini, Pascal Le Floch, Carlo Adamo[Ecole Nationale Supérieure de Chimie de Paris-Chimie ParisTech]

A computational study utilizing density functional theory (DFT) was performed to analyze the mechanism of ethylene dimerization catalyzed by (P,N) nickel(II) complexes, where (P,N) is a mixed phosphine–iminophosphorane ligand.

2119-2126 **Structural elucidation of supramolecular alpha-cyclodextrin dimer/aliphatic monofunctional molecules complexes,** L. Barrientos[Universidad Metropolitana de Ciencias de la Educación], E. Lang, G. Zapata-Torres, C. Celis-Barros, C. Orellana, P. Jara, N. Yutronic

The structural elucidation of 2α-cyclodextrin/1-octanethiol, 2α-cyclodextrin/1-octylamine and 2α-cyclodextrin/1-nonanoic acid inclusion complexes by nuclear magnetic resonance (NMR) spectroscopy and molecular modeling has been achieved.

2127-2142 **Investigation of the antioxidant properties of hyperjovinol A through its Cu(II) coordination ability,** Liliana Mammino[University of Venda]

Hyperjovinol A (2-methyl-1-(2,4,6-trihydroxy-3-(3-hydroxy-3,7-dimethyloct-6-enyl)phen yl)propan-1-one) is an acylated phloroglucinol isolated from *Hypericum Jovis* and exhibiting antioxidant properties comparable with those of the most common antioxidant drugs. The study models the compound's antioxidant ability through its ability to coordinate a Cu^{2+} ion and reduce it to Cu^{+}.

2143-2148 **Stability and electronic properties of 3D covalent organic frameworks,** Binit Lukose[Jacobs University Bremen], Agnieszka Kuc, Thomas Heine

Covalent organic frameworks (COFs) are a class of covalently linked crystalline nanoporous materials, versatile for nanoelectronic and storage applications. 3D COFs, in particular, have very large pores and low mass densities. Extensive theoretical studies of their energetic and mechanical stability, as well as their electronic properties, have been carried out for all known 3D COFs.

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1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

Monte Carlo Simulation Methods for Computing Liquid–Vapor Saturation Properties of Model Systems

Kaustubh S. Rane, Sabharish Murali, and Jeffrey R. Errington [The State University of New York]

J. Chem. Theor. and Comp, **9**, 2552-2566, 2013.

We discuss molecular simulation methods for computing the phase coexistence properties of complex molecules. The strategies that we pursue are histogram-based approaches in which thermodynamic properties are related to relevant probability distributions. We first outline grand canonical and isothermal–isobaric methods for directly locating a saturation point at a given temperature. In the former case, we show how reservoir and growth expanded ensemble techniques can be used to facilitate the creation and insertion of complex molecules within a grand canonical simulation.

Water and Solvation

Combination of COSMOmic and molecular dynamics simulations for the calculation of membrane-water partition coefficients

Sven Jakobtorweihen [Hamburg University of Technology] ,Thomas Ingram ,Irina Smirnova

J. Comp. Chem., **34**, 1332–1340, 2013.
A!

The importance of membrane-water partition coefficients led to the recent extension of the conductor-like screening model for realistic solvation (COSMO-RS) to micelles and biomembranes termed COSMOmic. Compared to COSMO-RS, this new approach needs structural information to account for the anisotropy of colloidal systems. This information can be obtained from molecular dynamics (MD) simulations. In this work, we show that this combination of molecular methods can efficiently be used to predict partition coefficients with good agreement to experimental data and enables screening studies.

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Water and Solvation (Cont'd)

Salting-in with a Salting-out Agent: Explaining the Cation Specific Effects on the Aqueous Solubility of Amino Acids

Luciana I. N. Tomé, Simão P. Pinho, Miguel Jorge, José R. B. Gomes, and João A. P. Coutinho [Universidade de Aveiro]

J. Phys. Chem. B., **117**, 6116–6128, 2013**.**

Although the understanding of ion specific effects on the aqueous solubilities of biomolecules is crucial for the development of many areas of biochemistry and life sciences, a consensual and well-supported molecular picture of the phenomena has not yet been established. Aiming at contributing to the understanding of the molecular-level mechanisms governing the cation specific effects on the aqueous solubilities of biocompounds, experimental solubility measurements and classical molecular dynamics simulations were performed for aqueous solutions of three amino acids (alanine, valine, and isoleucine), in the presence of a series of inorganic salts.

Analysis of Biomolecular Solvation Sites by 3D-RISM Theory

Daniel J. Sindhikara and Fumio Hirata [Ritsumeikan University]

J. Phys. Chem. B., **117**, 6718–6723, 2013**.**

We derive, implement, and apply equilibrium solvation site analysis for biomolecules. Our method utilizes 3D-RISM calculations to quickly obtain equilibrium solvent distributions without either necessity of simulation or limits of solvent sampling. Our analysis of these distributions extracts highest likelihood poses of solvent as well as localized entropies, enthalpies, and solvation free energies. We demonstrate our method on a structure of HIV-1 protease where excellent structural and thermodynamic data are available for comparison.

Probabilistic Approach to the Length-Scale Dependence of the Effect of Water Hydrogen Bonding on Hydrophobic Hydration

Y. S. Djikaev [Department of Chemical and Biological Engineering,SUNY at Buffalo]and E. Ruckenstein

J. Phys. Chem. B., **117**, 7015–7025, 2013**.**

We present a probabilistic approach to water–water hydrogen bonding that allows one to obtain an analytic expression for the number of bonds per water molecule as a function of both its distance to a hydrophobic particle and hydrophobe radius. This approach can be used in density functional theory (DFT) and computer simulations to examine particle size effects on the hydration of particles and on their solvent-mediated interaction. For example, it allows one to explicitly identify a water hydrogen bond contribution to the external potential, whereto a water molecule is subjected near a hydrophobe.

Molecular Insight into Different Denaturing Efficiency of Urea, Guanidinium, and Methanol: A Comparative Simulation Study

Takahiro Koishi, Kenji Yasuoka, Soohaeng Yoo Willow, Shigenori Fujikawa, and Xiao Cheng Zeng [University of Nebraska]

J. Chem. Theor. and Comp, **9**, 2540-2551, 2013.

We have designed various nanoslit systems, whose opposing surfaces can be either hydrophobic, hydrophilic, or simply a water-vapor interface, for the molecular dynamics simulation of confined water with three different protein denaturants, i.e., urea, guanidinium chloride (GdmCl), and methanol, respectively. Particular attention is placed on the preferential adsorption of the denaturant molecules onto the opposing surfaces and associated resident time in the vicinal layer next to the surfaces, as well as their implication in the denaturing efficiency of different denaturant molecules.

Medicinal Chemistry and Drug Design

Synthesis, biological evaluation, and molecular docking studies of novel 1,3,4-oxadiazole derivatives possessing benzotriazole moiety as FAK inhibitors with anticancer activity

Shuai Zhang, Yin Luo, Liang-Qiang He, Zhi-Jun Liu, Ai-Qin Jiang, Yong-Hua Yang, Hai-Liang Zhu[Nanjing University]

Bioorg. and Med.Chem., **21**, 3723–3729, 2013.

1,3,4-Oxadiazole derivatives have drawn continuing interest over the years because of their varied biological activities. In order to search for novel anticancer agents, we designed and synthesized a series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety as potential focal adhesion kinase (FAK) inhibitors. All the synthesized compounds were firstly reported. Among the compounds, compound **4** shows the most potent inhibitory activity against MCF-7 and HT29 cell lines with IC_{50} values of 5.68 μg/ml and 10.21 μg/ml, respectively. Besides, all the compounds were assayed for FAK inhibitory activity using the TRAP–PCR–ELISA assay.

Curcumin-I Knoevenagel's condensates and their Schiff's bases as anticancer agents: Synthesis, pharmacological and simulation studies

Imran Ali [Jamia Millia Islamia (Central University)], Ashanul Haque, Kishwar Saleem, Ming Fa Hsieh

Bioorg. and Med.Chem., **21**, 3808-3820, 2013.

Pyrazolealdehydes (4a–d), Knoevenagel's condensates (5a–d) and Schiff's bases (6a–d) of curcumin-I were synthesized, purified and characterized. Hemolysis assays, cell line activities, DNA bindings and docking studies were carried out. These compounds were lesser hemolytic than standard drug doxorubicin. Minimum cell viability (MCF-7; wild) observed was 59% (1.0 μg/mL) whereas the DNA binding constants ranged from 1.4×10^3 to 8.1×10^5 M^{-1}. The docking energies varied from −7.30 to −13.4 kcal/mol. It has been observed that DNA-compound adducts were stabilized by three governing forces (Van der Wall's, H-bonding and electrostatic attractions).

Prodrugs for masking bitter taste of antibacterial drugs—a computational approach

Rafik Karaman[Al-Quds University]

J. Mol.Mod., **19,** 2399-2412, 2013.

DFT calculations for the acid-catalyzed hydrolysis of several maleamic acid amide derivatives revealed that the reaction rate-limiting step is determined on the nature of the amine leaving group. Further, it was established that when the amine leaving group was a secondary amine, acyclovir or cefuroxime moiety the tetrahedral intermediate formation was the rate-limiting step such as in the cases of acyclovir **ProD 1- ProD 4** and cefuroxime **ProD 1- ProD 4**.

Highly SpecIfic and Sensitive Pharmacophore Model for Identifying CXCR4 Antagonists. Comparison with Docking and Shape-Matching Virtual Screening Performance

Arnaud S. Karaboga, Jesús M. Planesas, Florent Petronin, Jordi Teixidó, Michel Souchet, and Violeta I. Pérez-Nueno [Universitat Ramon Llull]

J.Chem. Infor. and Mod. **53**, 1043-1056, 2013.

HIV infection is initiated by fusion of the virus with the target cell through binding of the viral gp120 protein with the CD4 cell surface receptor protein and the CXCR4 or CCR5 coreceptors. There is currently considerable interest in developing novel ligands that can modulate the conformations of these coreceptors and, hence, ultimately block virus–cell fusion. Herein, we present a highly specific and sensitive pharmacophore model for identifying CXCR4 antagonists that could potentially serve as HIV entry inhibitors. Its performance was compared with docking and shape-matching virtual screening approaches using 3OE6 CXCR4 crystal structure and high-affinity ligands as query molecules, respectively.

Medicinal Chemistry and Drug Design (Cont'd)

Hit Expansion Approaches Using Multiple Similarity Methods and Virtualized Query Structures

Andreas Bergner [Chesterford Research Park]and Serge P. Parel

J.Chem. Infor. and Mod. **53**, 1057–1066, 2013.

Ligand-based virtual screening and computational hit expansion methods undoubtedly facilitate the finding of novel active chemical entities, utilizing already existing knowledge of active compounds. It has been demonstrated that the parallel execution of complementary similarity search methods enhances the performance of such virtual screening campaigns. In this article, we examine the use of virtualized template (query, seed) structures as an extension to common search methods, such as fingerprint and pharmacophore graph-based similarity searches.

Exploring the Potential of Protein-Based Pharmacophore Models in Ligand Pose Prediction and Ranking

Bingjie Hu and Markus A. Lill [Purdue University]

J.Chem. Infor. and Mod. **53**, 1179-1190, 2013.

Protein-based pharmacophore models derived from protein binding site atoms without the inclusion of any ligand information have become more popular in virtual screening studies. However, the accuracy of protein-based pharmacophore models for reproducing the critical protein–ligand interactions has never been explicitly assessed. In this study, we used known protein–ligand contacts from a large set of experimentally determined protein–ligand complexes to assess the quality of the protein-based pharmacophores in reproducing these critical contacts.

Identification of Substituted Pyrimido[5,4-b]indoles as Selective Toll-Like Receptor 4 Ligands

Michael Chan, Tomoko Hayashi, Richard D. Mathewson, Afshin Nour, Yuki Hayashi, Shiyin Yao, Rommel I. Tawatao, Brian Crain, Igor F. Tsigelny, Valentina L. Kouznetsova, Karen Messer, Minya Pu, Maripat Corr, Dennis A. Carson, and Howard B. Cottam [University of California]

J.Med.Chem., **56,** 4206–4223, 2013.

A cell-based high-throughput screen to identify small molecular weight stimulators of the innate immune system revealed substituted pyrimido[5,4-b]indoles as potent NFκB activators. The most potent hit compound selectively stimulated Toll-like receptor 4 (TLR4) in human and mouse cells. Synthetic modifications of the pyrimido[5,4-b]indole scaffold at the carboxamide, N-3, and N-5 positions revealed differential TLR4 dependent production of NFκB and type I interferon associated cytokines, IL-6 and interferon γ-induced protein 10 (IP-10) respectively.

Synthesis, Pharmacological Characterization, and Docking Analysis of a Novel Family of Diarylisoxazoles as Highly Selective Cyclooxygenase-1 (COX-1) Inhibitors

Paola Vitale, Stefania Tacconelli, Maria Grazia Perrone, Paola Malerba, Laura Simone, Antonio Scilimati, Antonio Lavecchia, Melania Dovizio, Emanuela Marcantoni, Annalisa Bruno, and Paola Patrignani [Center of Excellence on Aging (CeSI), Chieti,]

J.Med.Chem., **56,** 4277–4299 2013.

3-(5-Chlorofuran-2-yl)-5-methyl-4-phenylisoxazole (P6), a known selective cyclooxygenase-1 (COX-1) inhibitor, was used to design a new series of 3,4-diarylisoxazoles in order to improve its biochemical COX-1 selectivity and antiplatelet efficacy. Structure–activity relationships were studied using human whole blood assays for COX-1 and COX-2 inhibition in vitro, and results showed that the simultaneous presence of 5-methyl (or -CF3), 4-phenyl, and 5-chloro(-bromo or -methyl)furan-2-yl groups on the isoxazole core was essential for their selectivity toward COX-1. 3g, 3s, 3d were potent and selective COX-1 inhibitors that affected platelet aggregation in vitro through the inhibition of COX-1-dependent thromboxane (TX) A2.

Medicinal Chemistry and Drug Design (Cont'd)

Discovery of Novel STAT3 Small Molecule Inhibitors via in Silico Site-Directed Fragment-Based Drug Design

Wenying Yu, Hui Xiao, Jiayuh Lin, and Chenglong Li[The Ohio State University]

J.Med.Chem., **56,** 4402-4412, 2013.

Constitutive activation of signal transducer and activator of transcription 3 (STAT3) has been validated as an attractive therapeutic target for cancer therapy. To stop both STAT3 activation and dimerization, a viable strategy is to design inhibitors blocking its SH2 domain phosphotyrosine binding site that is responsible for both actions. A new fragment-based drug design (FBDD) strategy, in silico site-directed FBDD, was applied in this study. A designed novel compound, 5,8-dioxo-6-(pyridin-3-ylamino)-5,8-dihydronaphthalene-1-sulfonamide (LY5), was confirmed to bind to STAT3 SH2 by fluorescence polarization assay.

Structural Comparison of the Wild-Type and Drug-Resistant Mutants of the Influenza A M2 Proton Channel by Molecular Dynamics Simulations

Ruo-Xu Gu, Limin Angela Liu, Yong-Hua Wang [South China University of Technology], Qin Xu, and Dong-Qing Wei

J. Phys. Chem. B., **117**, 6042–6051, 2013**.**

The influenza A M2 channel in the viral envelope is a pH-regulated proton channel that is crucial for viral infection and replication. Amantadine and rimantadine are two M2 inhibitors that have been widely used as anti-influenza drugs. However, due to naturally occurring drug-resistant mutations, their inhibition ability has gradually decreased. Investigating the structures and the M2–inhibitor interactions of these mutants would illuminate drug inhibition and drug resistance mechanisms and guide the design of novel anti-influenza drugs targeting these drug-resistant mutants. In this study, we chose four mutations at different positions (V27A, S31N, L26F, L38F) and conducted molecular dynamics simulations on both the apo-form and the drug-bound forms.

Computationally Efficient Methodology for Atomic-Level Characterization of Dendrimer–Drug Complexes: A Comparison of Amine- and Acetyl-Terminated PAMAM

Ariela Vergara-Jaque, Jeffrey Comer, Luis Monsalve, Fernando D. González-Nilo, and Claudia Sandoval[Universidad Andres Bello]

J. Phys. Chem. B., **117**, 6801-6813, 2013**.**
A!

PAMAM dendrimers have been widely studied as a novel means for controlled drug delivery; however, computational study of dendrimer–drug complexation is made difficult by the conformational flexibility of dendrimers and the nonspecific nature of the dendrimer–drug interactions. In this work, we generate cavities in generation-5 polyamidoamine (PAMAM) dendrimers at selected distances from the center of mass of the dendrimer for the insertion of the model drug: dexamethasone 21-phosphate or Dp21.

Crystal Growth

Intermediate Structures for Higher Level Arrangements: Catching Disk-Like Micelles in Decane Phosphonic Acid Aqueous Solutions

Erica P. Schulz, Ángel Piñeiro, José L. Rodriguez, Rosana M. Minardi, Marisa Frechero, and Pablo C. Schulz [Universidad Nacional del Su]

J. Phys. Chem. B., **117**, 6231–6240, 2013**.**

It has been proposed that disk-like micelles may be precursors to the formation of lamellar liquid crystals. The possibility of obtaining n-decane phosphonic acid (DPA) disk-like micelles in aqueous solution without the addition of a second ionic surfactant led us to study in detail the low-concentration range of this system by both a battery of experimental techniques and molecular dynamics (MD) simulations. The experimental results indicate that premicelles with some capacity to solubilize dyes are formed at 0.05 mM. The critical micelle concentration (cmc) was found to be 0.260 ± 0.023 mM, much lower than that previously reported in the literature. Spherical micelles, which immediately grow, leading to disk-like micelles, are probably formed at this concentration.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

A novel web server predicts amino acid residue protection against hydrogen–deuterium exchange

Mikhail Yu. Lobanov, Masha Yu. Suvorina, Nikita V. Dovidchenko, Igor V. Sokolovskiy, Alexey K. Surin, and Oxana V. Galzitskaya[State Research Center for Applied Microbiology & Biotechnology, Moscow Region]

Bioinformatics. **29**, 1375-1381, 2013.

To clarify the relationship between structural elements and polypeptide chain mobility, a set of statistical analyses of structures is necessary. Because at present proteins with determined spatial structures are much less numerous than those with amino acid sequence known, it is important to be able to predict the extent of proton protection from hydrogen–deuterium (HD) exchange basing solely on the protein primary structure. Here we present a novel web server aimed to predict the degree of amino acid residue protection against HD exchange solely from the primary structure of the protein chain under study. On the basis of the amino acid sequence, the presented server offers the following three possibilities (predictors) for user's choice.

Biographer: web-based editing and rendering of SBGN compliant biochemical networks

Falko Krause, Marvin Schulz, Ben Ripkens, Max Flöttmann, Marcus Krantz, Edda Klipp, and Thomas Handorf [Humboldt-Universität zu Berlin]

Bioinformatics. **29**, 1467-1468, 2013.

The rapid accumulation of knowledge in the field of Systems Biology during the past years requires advanced, but simple-to-use, methods for the visualization of information in a structured and easily comprehensible manner. We have developed biographer, a web-based renderer and editor for reaction networks, which can be integrated as a library into tools dealing with network-related information. Our software enables visualizations based on the emerging standard Systems Biology Graphical Notation.

Bioinformatics and Cheminformatics (Cont'd)

Predicting the functional consequences of cancer-associated amino acid substitutions

Hashem A. Shihab, Julian Gough, David N. Cooper [Cardiff University], Ian N. M. Day, and Tom R. Gaunt

Bioinformatics. **29**, 1504-1510, 2013.

The number of missense mutations being identified in cancer genomes has greatly increased as a consequence of technological advances and the reduced cost of whole-genome/whole-exome sequencing methods. In our previous work, we developed the Functional Analysis through Hidden Markov Models (FATHMM) software and, using a model weighted for inherited disease mutations, observed improved performances over alternative computational prediction algorithms. Here, we describe an adaptation of our original algorithm that incorporates a cancer-specific model to potentiate the functional analysis of driver mutations.

HOMECAT: consensus homologs mapping for interspecific knowledge transfer and functional genomic data integration

Simone Zorzan [University of Verona], Erika Lorenzetto, Michele Ettorre, Valeria Pontelli, Carlo Laudanna, and Mario Buffelli

Bioinformatics. **29**, 1574-1576, 2013.

Comparative studies are encouraged by the fast increase of data availability from the latest high-throughput techniques, in particular from functional genomic studies. Yet, the size of datasets, the challenge of complete orthologs findings and not last, the variety of identification formats, make information integration challenging. With HOMECAT, we aim to facilitate cross-species relationship identification and data mapping, by combining orthology predictions from several publicly available sources, a convenient interface for high-throughput data download and automatic identifier conversion into a Cytoscape plug-in, that provides both an integration with a large set of bioinformatics tools, as well as a user-friendly interface.

INstruct: a database of high-quality 3D structurally resolved protein interactome networks

Michael J. Meyer, Jishnu Das, Xiujuan Wang, and Haiyuan Yu [Cornell University]

Bioinformatics. **29**, 1577-1579, 2013.

INstruct is a database of high-quality, 3D, structurally resolved protein interactome networks in human and six model organisms. INstruct combines the scale of available high-quality binary protein interaction data with the specificity of atomic-resolution structural information derived from co-crystal evidence using a tested interaction interface inference method. Its web interface is designed to allow for flexible search based on standard and organism-specific protein and gene-naming conventions, visualization of protein architecture highlighting interaction interfaces and viewing and downloading custom 3D structurally resolved interactome datasets.

JACOB: An enterprise framework for computational chemistry

Mark P. Waller [Westfälische Wilhelms Universität Münster,],Thomas Dresselhaus,Jack Yang

J. Comp. Chem., **34**, 1420–1428, 2013.

Here, we present just a collection of beans (JACOB): an integrated batch-based framework designed for the rapid development of computational chemistry applications. The framework expedites developer productivity by handling the generic infrastructure tier, and can be easily extended by user-specific scientific code. Paradigms from enterprise software engineering were rigorously applied to create a scalable, testable, secure, and robust framework.

Protein Secondary Structure

Simultaneous prediction of protein secondary structure and transmembrane spans

Julia Koehler Leman,, Ralf Mueller, Mert Karakas, Nils Woetzel and Jens Meiler[Vanderbilt University]

Proteins: Stru. Fun. & Bioinf., **81**, 1127–1140, 2013.

Prediction of transmembrane spans and secondary structure from the protein sequence is generally the first step in the structural characterization of (membrane) proteins. Preference of a stretch of amino acids in a protein to form secondary structure and being placed in the membrane are correlated. Nevertheless, current methods predict either secondary structure or individual transmembrane states. We introduce a method that simultaneously predicts the secondary structure and transmembrane spans from the protein sequence.

Comparative or Homology Modeling

An NMDA Receptor Gating Mechanism Developed from MD Simulations Reveals Molecular Details Underlying Subunit-Specific Contributions

Jian Dai, Huan-Xiang Zhou [Florida State University]

Biophysical Journal. **104**, 2170–2181, 2013.

A!

N-methyl-D-aspartate (NMDA) receptors are obligate heterotetrameric ligand-gated ion channels that play critical roles in learning and memory. Here, using targeted molecular dynamics simulations, we developed an atomistic model for the gating of the GluN1/GluN2A NMDA receptor. Upon agonist binding, lobe closure of the ligand-binding domain produced outward pulling of the M3-D2 linkers, leading to outward movements of the C-termini of the pore-lining M3 helices and opening of the channel.

Bending Free Energy from Simulation: Correspondence of Planar and Inverse Hexagonal Lipid Phases

Alexander J. Sodt, Richard W. Pastor [National Institutes of Health, Rockville]

Biophysical Journal. **104**, 2202–2211, 2013.

Simulations of two distinct systems, one a planar bilayer, the other the inverse hexagonal phase, indicate consistent mechanical properties and curvature preferences, with single DOPE leaflets having a spontaneous curvature, $R_0 = -26$ Å (experimentally ~–29.2 Å) and DOPC leaflets preferring to be approximately flat ($R_0 = -65$ Å, experimentally ~–87.3 Å). Additionally, a well-defined pivotal plane, where a DOPE leaflet bends at constant area, has been determined to be near the glycerol region of the lipid, consistent with the experimentally predicted plane.

Homology modeling, ligand docking and in silico mutagenesis of neurospora Hsp80 (90): insight into intrinsic ATPase activity

Samir S. Roy, Robert W. Wheatley, Manju Kapoor [The University of Calgary,]

J. Mol.Graph. and Mod., **42,** 54–69, 2013.

The Hsp90 family of proteins is an important component of the cellular response to elevated temperatures, environmental or physiological stress and nuclear receptor signalling. The primary object of this work is the 80-kDa heat shock protein, a member of the Hsp90 family, from the model filamentous fungus Neurospora crassa, (henceforth referred to as Hsp80Nc). In contrast to more extensively characterized members of the same family, (e.g. Hsp82Sc of Saccharomyces cerevisiae) it exhibits a higher intrinsic ATPase activity and the ability to form hetero-oligomeric complexes with Hsp70 in the absence of co-chaperones or other ancillary factors.

Protein Confirmational Analysis

Intramolecular hydrogen-bonding in aqueous carbohydrates as a cause or consequence of conformational preferences: a molecular dynamics study of cellobiose stereoisomers

Dongqi Wang, Maria Lovísa Ámundadóttir, Wilfred F. van Gunsteren, Philippe H. Hünenberger [Swiss Federal Institute of Technology]

Euro.biophy. jour., **42**, 521-537, 2013.

It is often assumed that intramolecular hydrogen-bonding (H-bonding) exerts a significant influence on the conformational properties of aqueous (bio-)polymers. To discuss this statement, one should, however, distinguish between solvent-exposed and buried H-bonds, and between their respective roles in promoting stability (i.e., as a driving force) and specificity (for which the term steering force is introduced here). In this study, the role of solvent-exposed H-bonding in carbohydrates as a driving or steering force is probed using explicit-solvent molecular dynamics simulations with local elevation umbrella sampling in the simple context of cellobiose stereoisomers.

Characterization of the internal dynamics and conformational space of zinc-bound amyloid β peptides by replica-exchange molecular dynamics simulations

Liang Xu [Dalian University of Technology**]**, Xiaojuan Wang, Xicheng Wang

Euro.biophy. jour., **42**, 575-586, 2013.

Amyloid β (Aβ) peptides and metal ions have been associated with the pathogenesis of Alzheimer's disease. The conformational space of Aβ fragments of different length with and without binding of metal ions has been extensively investigated by replica-exchange molecular dynamics (REMD) simulation. The capability of REMD simulations to characterize the internal dynamics of such intrinsically disordered proteins (IDPs) as Aβ has been overlooked. In this work, we use an approach recently developed by Xue and Skrynnikov (J Am Chem Soc 133:14614–14628, 2011) to calculate NMR observables, including ^{15}N relaxation rates and ^{15}N–^{1}H nuclear Overhauser enhancement (NOE), from the high-temperature trajectory of REMD simulations for zinc-bound Aβ peptides.

Conformational Determinants of the Activity of Antiproliferative Factor Glycopeptide

Sairam S. Mallajosyula, Kristie M. Adams, Joseph J. Barchi, and Alexander D. MacKerell [University of Maryland]

J.Chem. Infor. and Mod. **53**, 1127–1137, 2013.

The antiproliferative factor (APF) involved in interstitial cystitis is a glycosylated nonapeptide (TVPAAVVVA) containing a sialylated core 1 α-O-disaccharide linked to the N-terminal threonine. The chemical structure of APF was deduced using spectroscopic techniques and confirmed using total synthesis. The synthetic APF provided a platform to study amino acid modifications and their effect on APF activity, based on which a structure–activity relationship (SAR) for APF activity was previously proposed. Presented is computational analysis of 14 APF derivatives to identify structural trends from which a more detailed SAR is obtained.

Protein Confirmational Analysis (Cont'd)

Unraveling the Allosteric Inhibition Mechanism of PTP1B by Free Energy Calculation Based on Umbrella Sampling

Wei Cui, Yuan-Hua Cheng, Ling-Ling Geng, Den-Sheng Liang, Ting-Jun Hou [Zhejiang University] and Ming-Juan Ji

J.Chem. Infor. and Mod. **53**, 1157–1167, 2013.

Protein tyrosine phosphatase 1B (PTP1B) is a promising target for the treatment of obesity and type II diabetes. Allosteric inhibitors can stabilize an active conformation of PTP1B by hindering the conformational transition of the WPD loop of PTP1B from the open to the closed state. Here, the umbrella sampling molecular dynamics (MD) simulations were employed to compute the reaction path of the conformational transition of PTP1B, and the snapshots extracted from the MD trajectory were clustered into 58 conformational groups based on the key conformational parameter.

Efficiency of Adaptive Temperature-Based Replica Exchange for Sampling Large-Scale Protein Conformational Transitions

Weihong Zhang and Jianhan Chen [State University, Manhattan, Kansas]

J. Chem. Theor. and Comp, **9**, 2849–2856, 2013.

A!

Temperature-based replica exchange (RE) is now considered a principal technique for enhanced sampling of protein conformations. It is also recognized that existence of sharp cooperative transitions (such as protein folding/unfolding) can lead to temperature exchange bottlenecks and significantly reduce the sampling efficiency. Here, we revisit two adaptive temperature-based RE protocols, namely, exchange equalization (EE) and current maximization (CM), that were previously examined using atomistic simulations (Lee and Olson, J. Chem. Physics2011, 134, 24111). Both protocols aim to overcome exchange bottlenecks by adaptively adjusting the simulation temperatures, either to achieve uniform exchange rates (in EE) or to maximize temperature diffusion (CM).

NMR Relaxation in Proteins with Fast Internal Motions and Slow Conformational Exchange: Model-Free Framework and Markov State Simulations

Junchao Xia, Nan-jie Deng, and Ronald M. Levy [Rutgers, the State University of New Jersey]

J. Phys. Chem. B., **117**, 6625–6634, 2013**.**

Calculating NMR relaxation effects for proteins with dynamics on multiple time scales generally requires very long trajectories based on conventional molecular dynamics simulations. In this report, we have built Markov state models from multiple MD trajectories and used the resulting MSM to capture the very fast internal motions of the protein within a free energy basin on a time scale up to hundreds of picoseconds and the more than 3 orders of magnitude slower conformational exchange between macrostates.

Detecting selection for negative design in proteins through an improved model of the misfolded state

Jonas Minning, Markus Porto and Ugo Bastolla[c. Nicolas Cabrera 1 Universidad,]

Proteins: Stru. Fun. & Bioinf., **81**, 1102–1112, 2013.

Proteins that need to be structured in their native state must be stable both against the unfolded ensemble and against incorrectly folded (misfolded) conformations with low free energy. Positive design targets the first type of stability by strengthening native interactions. The second type of stability is achieved by destabilizing interactions that occur frequently in the misfolded ensemble, a strategy called negative design. We investigate negative design adopting a statistical mechanical model of the misfolded ensemble, which improves the usual Gaussian approximation by taking into account the third moment of the energy distribution and contact correlations.

Protein Confirmational Analysis (Cont'd)

Molecular dynamics simulations of transitions for ECD epidermal growth factor receptors show key differences between human and drosophila forms of the receptors

Juan R. Perilla, Daniel J. Leahy and Thomas B. Woolf[Johns Hopkins University,]

Proteins: Stru. Fun. & Bioinf., **81**, 1113–1126, 2013.
A!

Recent X-ray structural work on the Drosophila epidermal growth factor receptor (EFGR) has suggested an asymmetric dimer that rationalizes binding affinity measurements that go back decades. This type of asymmetric structure has not been seen for the human EGF receptor family and it may or may not be important for function in that realm. We hypothesize that conformational changes in the Drosophila system have been optimized for the transition, whereas the barrier for the same transition is much higher in the human forms.

Protein Structure Analysis

Influence of C-terminal tail deletion on structure and stability of hyperthermophile Sulfolobus tokodaii RNase HI

Lin Chen, Ji-Long Zhang, Qing-Chuan Zheng, Wen-Ting Chu, Qiao Xue, Hong-Xing Zhang [Jilin University], Chia-Chung Sun

J. Mol.Mod., **19,** 2647-2656, 2013.

The C-terminus tail (G144-T149) of the hyperthermophile *Sulfolobus tokodaii* (Sto-RNase HI) plays an important role in this protein's hyperstabilization and may therefore be a good protein stability tag. Focused on*Sulfolobus tokodaii* RNase HI (Sto-RNase HI) and its derivative lacking the C-terminal tail (ΔC6 Sto-RNase HI) (PDB codes: 2EHG and 3ALY), we applied molecular dynamics (MD) simulations at four different temperatures (300, 375, 475, and 500 K) to examine the effect of the C-terminal tail on the hyperstabilization of Sto-RNase HI and to investigate the unfolding process of Sto-RNase HI and ΔC6 Sto-RNase HI.

Statistical torsion angle potential energy functions for protein structure modeling: A bicubic interpolation approach

Tae-Rae Kim, Joshua SungWoo Yang, Seokmin Shin and Jinhyuk Lee[Korean Bioinformation Center (KOBIC)]

Proteins: Stru. Fun. & Bioinf., **81**, 1156–1165, 2013.

A set of grid type knowledge-based energy functions is introduced for ϕ–$\chi1$, ψ–$\chi1$, ϕ–ψ, and $\chi1$–$\chi2$ torsion angle combinations. Boltzmann distribution is assumed for the torsion angle populations from protein X-ray structures, and the functions are named as statistical torsion angle potential energy functions. The grid points around periodic boundaries are duplicated to force periodicity, and the remedy relieves the derivative discontinuity problem. The devised functions rapidly improve the quality of model structures.

Protein Dynamics

Role of Dimerization Efficiency of Transmembrane Domains in Activation of Fibroblast Growth Factor Receptor 3

Pavel E. Volynsky, Anton A. Polyansky [Russian Academy of Sciences], Gulfia N. Fakhrutdinova, Eduard V. Bocharov, and Roman G. Efremov

J. Am. Chem. Soc., 2013, **135**, 8105-8108

Mutations in transmembrane (TM) domains of receptor tyrosine kinases are shown to cause a number of inherited diseases and cancer development. Here, we use a combined molecular modeling approach to understand molecular mechanism of effect of G380R and A391E mutations on dimerization of TM domains of human fibroblast growth factor receptor 3 (FGFR3). According to results of Monte Carlo conformational search in the implicit membrane and further molecular dynamics simulations, TM dimer of this receptor is able to form a number of various conformations, which differ significantly by the free energy of association in a full-atom model bilayer.

Characterizing the Membrane-Bound State of Cytochrome P450 3A4: Structure, Depth of Insertion, and Orientation

Javier L. Baylon, Ivan L. Lenov, Stephen G. Sligar, and Emad Tajkhorshid [University of Illinois at Urbana−Champaign]

J. Am. Chem. Soc., 2013, **135**, 8542-8551
A!

Cytochrome P450 3A4 (CYP3A4) is the most abundant membrane-associated isoform of the P450 family in humans and is responsible for biotransformation of more than 50% of drugs metabolized in the body. Despite the large number of crystallographic structures available for CYP3A4, no structural information for its membrane-bound state at an atomic level is available. In order to characterize binding, depth of insertion, membrane orientation, and lipid interactions of CYP3A4, we have employed a combined experimental and simulation approach in this study. Taking advantage of a novel membrane representation, highly mobile membrane mimetic (HMMM), with enhanced lipid mobility and dynamics.

Transient Access to the Protein Interior: Simulation versus NMR

Filip Persson and Bertil Halle [Lund University]

J. Am. Chem. Soc., 2013, **135**, 8735-8748

Many proteins rely on rare structural fluctuations for their function, whereby solvent and other small molecules gain transient access to internal cavities. In magnetic relaxation dispersion (MRD) experiments, water molecules buried in such cavities are used as intrinsic probes of the intermittent protein motions that govern their exchange with external solvent. While this has allowed a detailed characterization of exchange kinetics for several proteins, little is known about the exchange mechanism. Here, we use a millisecond all-atom MD trajectory produced by Shaw et al. (Science2010, 330, 341) to characterize water exchange from the four internal hydration sites in the protein bovine pancreatic trypsin inhibitor.

Protein Dynamics (Cont'd)

An implementation of hydrophobic force in implicit solvent molecular dynamics simulation for packed proteins

Li L. Duan, Tong Zhu, Ye Mei, Qing G. Zhang, Bo Tang, John Z. H. Zhang[East China Normal University]

J. Mol.Mod., **19,** 2605-2612 2013.

MD simulations of five proteins in which helical chains are held together by hydrophobic packing were carried out to investigate the effect of hydrophobic force on simulated structures of these protein complexes in implicit generalized Born (GB) model. The simulation study employed three different methods to treat hydrophobic effect: the standard GB method that does not include explicit hydrophobic force, the LCPO method that includes explicit hydrophobic force based directly on solvent accessible surface area (SASA), and a proposed packing enforced GB (PEGB) method that includes explicit hydrophobic force based on the radius of gyration of the protein complex.

A Charge Moving Algorithm for Molecular Dynamics Simulations of Gas-Phase Proteins

Sarah K. Fegan and Mark Thachuk [University of British Columbia]

J. Chem. Theor. and Comp, **9**, 2531–2539, 2013.

A method for moving charges in a coarse-grained simulation of gas-phase proteins is presented which uses a Monte Carlo approach to move charges between charge sites. The method is used to study the role of charge movement in the dissociation mechanism of protein complexes in order to better understand experimentally observed mass spectra from CID studies. The charge hopping process is analyzed using energy distributions and a pair correlation plot. Hopping rates, charge distributions, and structural parameters (radius of gyration and RMSD) are also calculated.

Analysis of Protein Dynamics Simulations by a Stochastic Point Process Approach

Bertil Halle [Lund University] and Filip Persson

J. Chem. Theor. and Comp, **9**, 2838–2848, 2013.

MD simulations can now explore the complex dynamics of proteins and their associated solvent in atomic detail on a millisecond time scale. Among the phenomena that thereby become amenable to detailed study are intermittent conformational transitions where the protein accesses transient high-energy states that often play key roles in biology. Here, we present a coherent theoretical framework, based on the stochastic theory of stationary point processes, that allows the essential dynamical characteristics of such processes to be efficiently extracted from the MD trajectory without assuming Poisson statistics.

Protein Dynamics (Cont'd)

Disentangling Electron Tunneling and Protein Dynamics of Cytochrome c through a Rationally Designed Surface Mutation

Damián Alvarez-Paggi, Wiebke Meister, Uwe Kuhlmann, Inez Weidinger, Katalin Tenger, László Zimányi, Gábor Rákhely, Peter Hildebrandt, and Daniel H. Murgida [Universidad de Buenos Aires]

J. Phys. Chem. B., **117**, 6061–6068, 2013**.**

Nonexponential distance dependence of the apparent electron-transfer (ET) rate has been reported for a variety of redox proteins immobilized on biocompatible electrodes, thus posing a physicochemical challenge of possible physiological relevance. We have recently proposed that this behavior may arise not only from the structural and dynamical complexity of the redox proteins but also from their interplay with strong electric fields present in the experimental setups and in vivo (J. Am Chem. Soc. 2010, 132, 5769−5778). Here we present a combined computational and experimental study of WT cytochrome c and the surface mutant K87C adsorbed on electrodes coated with self-assembled monolayers (SAMs) of varying thickness.

Hydrodynamic Effects on the Relative Rotational Velocity of Associating Proteins

Maciej Długosz [University of Warsaw]and Jan M. Antosiewicz

J. Phys. Chem. B., **117**, 6165–6174, 2013**.**

Hydrodynamic steering effects on the barnase–barstar association were studied through the analysis of the relative rotational velocity of the proteins. We considered the two proteins approaching each other in response to their electrostatic attraction and employed a method that accounts for the long-range and many-body character of the hydrodynamic interactions, as well as the complicated shapes of the proteins. Hydrodynamic steering effects were clearly seen when attractive forces were applied to the geometric centers of the proteins (resulting in zero torques) and the attraction acted along the line that connects centers of geometry of proteins in their crystallographic complex.

Single Point Mutation Alters the Microstate Dynamics of Amyloid β-Protein Aβ42 as Revealed by Dihedral Dynamics Analyses

Liang Xu [Dalian University of Technology,], Shengsheng Shan, and Xicheng Wang

J. Phys. Chem. B., **117**, 6206–6216, 2013**.**

The aggregation of amyloid β-protein (Aβ) has been associated with the pathogenesis of Alzheimer's disease. A number of single point mutations at residues A21, E22, D23, and M35 have been identified to show increased or decreased aggregation tendency. In this work, dihedral dynamics analyses, which combine dihedral principle component analysis (dPCA), potential of mean force (PMF) calculations, and Markov state models (MSMs), were proposed to elucidate the different global free energy landscapes (FELs), the PMF of individual dihedral angle, and microstates/macrostates for a number of Aβ42 mutants (Flemish A21G, Arctic E22G, Italian E22K, Dutch E22Q, Iowa D23N, Japanese E22Δ, and M35 oxidation Met35OX).

Protein Dynamics (Cont'd)

Effect of Ionic Aqueous Environments on the Structure and Dynamics of the Aβ21–30 Fragment: A Molecular-Dynamics Study

Micholas Dean Smith and Luis Cruz [Drexel University]

J. Phys. Chem. B., **117**, 6614–6624, 2013**.**

The amyloid β-protein (Aβ) has been implicated in the pathogenesis of Alzheimer's disease. The role of the structure and dynamics of the central Aβ21–30 decapeptide region of the full-length Aβ is considered crucial in the aggregation pathway of Aβ. Here we report results of isobaric–isothermal (NPT) all-atom explicit water molecular dynamics simulations of the monomeric form of the wild-type Aβ21–30 fragment in aqueous salt environments formed by neurobiologically important group IA (NaCl, KCl) and group IIA (CaCl2, MgCl2) salts.

Simulation of Two-Dimensional Sum-Frequency Generation Response Functions: Application to Amide I in Proteins

Chungwen Liang and Thomas L. C. Jansen [University of Groningen]

J. Phys. Chem. B., **117**, 6937–6945, 2013**.**

We present the implementation of an approach to simulate the two-dimensional sum frequency generation response functions of systems with numerous coupled chromophores using a quantum-classical simulation scheme that was previously applied successfully to simulate two-dimensional infrared spectra. We apply the simulation to the amide I band of a mechanosensitive channel protein. By examining the signal generated from different segments of the protein, we find that the overall signal is impossible to interpret without the aid of simulations due to the interference of the response generated on different segments of the protein.

Thermodynamic analysis of structural transitions during GNNQQNY aggregation

Kenneth L. Osborne, Michael Bachmann and Birgit Strodel[Research Centre Jülich,]

Proteins: Stru. Fun. & Bioinf., **81**, 1141–1155, 2013.

Amyloid protein aggregation characterizes many neurodegenerative disorders, including Alzheimer's, Parkinson's, and Creutzfeldt-Jakob disease. Evidence suggests that amyloid aggregates may share similar aggregation pathways, implying simulation of full-length amyloid proteins is not necessary for understanding amyloid formation. In this study, we simulate GNNQQNY, the N-terminal prion-determining domain of the yeast protein Sup35 to investigate the thermodynamics of structural transitions during aggregation. Utilizing a coarse-grained model permits equilibration on relevant time scales.

Free Energy Calculations

Free-energy differences between states with different conformational ensembles

Jose Antonio Garate, Chris Oostenbrink [University of Natural Resources and Life Sciences, Vienna]

J. Comp. Chem., **34**, 1398–1408, 2013.

Multiple conformations separated by high-energy barriers represent a challenging problem in free-energy calculations due to the difficulties in achieving adequate sampling. We present an application of thermodynamic integration (TI) in conjunction with the local elevation umbrella sampling (LE/US) method to improve convergence in alchemical free-energy calculations. TI-LE/US was applied to the guanosine triphosphate (GTP) to 8-Br-GTP perturbation, molecules that present high-energy barriers between the anti and syn states and that have inverted preferences for those states.

Free Energy Calculations (Cont'd)

Prediction of Phase Equilibrium and Hydration Free Energy of Carboxylic Acids by Monte Carlo Simulations

Nicolas Ferrando [IFP Energies Nouvelles], Ibrahim Gedik, Véronique Lachet, Laurent Pigeon, and Rafael Lugo

J. Phys. Chem. B., **117**, 7123–7132, 2013**.**

In this work, a new transferable united-atom force field has been developed to predict phase equilibrium and hydration free energy of carboxylic acids. To take advantage of the transferability of the AUA4 force field, all Lennard-Jones parameters of groups involved in the carboxylic acid chemical function are reused from previous parametrizations of this force field. Only a unique set of partial electrostatic charges is proposed to reproduce the experimental gas phase dipole moment, saturated liquid densities and vapor pressures.

Ligand Binding/Docking

Dynamic combinatorial libraries of artificial repeat proteins

Margarita Eisenberg, Inbal Shumacher, Rivka Cohen-Luria, Gonen Ashkenasy [Ben Gurion University of the Negev]

Bioorg. and Med.Chem., **21**, 3450–3457, 2013.

Repeat proteins are found in almost all cellular systems, where they are involved in diverse molecular recognition processes. Recent studies have suggested that de novo designed repeat proteins may serve as universal binders, and might potentially be used as practical alternative to antibodies. We describe here a novel chemical methodology for producing small libraries of repeat proteins, and screening in parallel the ligand binding of library members.

Drug Uptake Pathways of Multidrug Transporter AcrB Studied by Molecular Simulations and Site-Directed Mutagenesis Experiments

Xin-Qiu Yao, Nobuhiro Kimura, Satoshi Murakami, and Shoji Takada [Kyoto University,]

J. Am. Chem. Soc., 2013, **135**, 7474–7485

Multidrug resistance has been a critical issue in current chemotherapy. In Escherichia coli, a major efflux pump responsible for the multidrug resistance contains a transporter AcrB. Crystallographic studies and mutational assays of AcrB provided much of structural and overall functional insights, which led to the functionally rotating mechanism. However, the drug uptake pathways are somewhat controversial because at least two possible pathways, the vestibule and the cleft paths, were suggested. Here, combining molecular simulations and site-directed mutagenesis experiments, we addressed the uptake mechanism finding that the drug uptake pathways can be significantly different depending on the properties of drugs.

Ligand Binding / Docking (Cont'd)

Ligand-Dependent Activation and Deactivation of the Human Adenosine A2A Receptor

Jianing Li, Amanda L. Jonsson, Thijs Beuming, John C. Shelley, and Gregory A. Voth [The University of Chicago]

J. Am. Chem. Soc., 2013, **135**, 8749-8759

G-protein-coupled receptors (GPCRs) are membrane proteins with critical functions in cellular signal transduction, representing a primary class of drug targets. Acting by direct binding, many drugs modulate GPCR activity and influence the signaling pathways associated with numerous diseases. However, complete details of ligand-dependent GPCR activation/deactivation are difficult to obtain from experiments. Therefore, it remains unclear how ligands modulate a GPCR's activity. To elucidate the ligand-dependent activation/deactivation mechanism of the human adenosine A2A receptor (AA2AR), a member of the class A GPCRs, we performed large-scale unbiased molecular dynamics and metadynamics simulations of the receptor embedded in a membrane.

The flexibility of P-glycoprotein for its poly-specific drug binding from molecular dynamics simulations

Ming Liu, Tingjun Hou, Zhiwei Feng & Youyong Li [Soochow University]

J. Biomol. Stru. and Dyn., 31,(6) 612-629,2013.
A!

The multidrug efflux pump P-glycoprotein (P-gp) contributes to multidrug resistance in about half of human cancers. Recently, high resolution X-ray crystal structures of mouse P-gp (inward-facing) were reported, which significantly facilitates the understanding of the function of P-gp and the structure-based design of inhibitors for P-gp. Here we perform 20 ns molecular dynamics simulations of inward-facing P-gp with/without ligand in explicit lipid and water to investigate the flexibility of P-gp for its poly-specific drug binding.

Modeling peptide binding to anionic membrane pores

Yi He, Lidia Prieto , Themis Lazaridis[City College of New York]

J. Comp. Chem., **34**, 1463–1475, 2013.

Peptide-induced pore formation in membranes can be dissected into two steps: pore formation and peptide binding to the pore. A computational method is proposed to study the second step in anionic membranes. The electrostatic potential is obtained from numerical solutions to the Poisson–Boltzmann equation and is then used in conjunction with IMM1 (implicit membrane model 1). A double charge layer model is used to incorporate the effects of the membrane dipole potential.

Conserved water mediated H-bonding dynamics of Ser117 and Thr119 residues in human transthyretin–thyroxin complexation: Inhibitor modeling study through docking and molecular dynamics simulation

Avik Banerjee, Hridoy R. Bairagya, Bishnu P. Mukhopadhyay [National Institute of Technology-Durgapur] , Tapas K. Nandi, Deepak K. Mishra

J. Mol.Graph. and Mod., **42,** 70–80, 2013.

Transthyretin (TTR) is a protein whose aggregation and deposition causes amyloid diseases in human beings. Amyloid fibril formation is prevented by binding of thyroxin (T4) or its analogs to TTR. The MD simulation study of several solvated X-ray structures of apo and holo TTR has indicated the role of a conserved water molecule and its interaction with T4 binding residues Ser117 and Thr119. Geometrical and electronic consequences of those interactions have been exploited to design a series of thyroxin analogs (Mod1–4) by modifying 5′ or 3′ or both the iodine atoms of thyroxin.

Ligand Binding / Docking (Cont'd)

Molecular dynamic simulations give insight into the mechanism of binding between 2-aminothiazole inhibitors and CDK5

Wei Wang, Xiaoning Cao, Xiaolei Zhu [Nanjing University of Technology,], Yongliang Gu

J. Mol.Mod., **19,** 2635-2645, 2013.

Molecular docking, molecular dynamics (MD) simulations, and binding free energy analysis were performed to reveal differences in the binding affinities between five 2-aminothiazole inhibitors and CDK5. The hydrogen bonding and hydrophobic interactions between inhibitors and adjacent residues are analyzed and discussed. . The rank of calculated binding free energies using the MM-PBSA method is consistent with experimental result. The results illustrate that hydrogen bonds with Cys83 favor inhibitor binding.

Molecular Dynamics Simulations of the Adenosine A2a Receptor: Structural Stability, Sampling, and Convergence

Hui Wen Ng, Charles A. Laughton, and Stephen W. Doughty [University of Nottingham Malaysia Campus]

J.Chem. Infor. and Mod. **53**, 1168–1178, 2013.

Molecular dynamics (MD) simulations of membrane-embedded G-protein coupled receptors (GPCRs) have rapidly gained popularity among the molecular simulation community in recent years, a trend which has an obvious link to the tremendous pharmaceutical importance of this group of receptors and the increasing availability of crystal structures. In view of the widespread use of this technique, it is of fundamental importance to ensure the reliability and robustness of the methodologies so they yield valid results and enable sufficiently accurate predictions to be made. In this work, 200 ns simulations of the A2a adenosine receptor (A2a AR) have been produced and evaluated in the light of these requirements.

Oxygen Entry through Multiple Pathways in T-State Human Hemoglobin

Masayoshi Takayanagi, Ikuo Kurisaki, and Masataka Nagaoka [Nagoya University]

J. Phys. Chem. B., **117**, 4254–4262, 2013**.**

The heme oxygen (O2) binding site of human hemoglobin (HbA) is buried in the interior of the protein, and there is a debate over the O2 entry pathways from solvent to the binding site. As a first step to understand HbA O2 binding process at the atomic level, we detected all significant multiple O2 entry pathways from solvent to the binding site in the α and β subunits of the T-state tetramer HbA by utilizing ensemble molecular dynamics (MD) simulation. By executing 128 independent 8 ns MD trajectories in O2-rich aqueous solvent, we simulated the O2 entry processes and obtained 141 and 425 O2 entry events in the α and β subunits of HbA, respectively.

Binding Mechanism of Inositol Stereoisomers to Monomers and Aggregates of Aβ(16-22)

Grace Li and Régis Pomès [The Hospital for Sick Children, Toronto,]

J. Phys. Chem. B., **117**, 6603–6613, 2013**.**

Alzheimer's disease (AD) is a severe neurodegenerative disease with no cure. A potential therapeutic approach is to prevent or reverse the amyloid formation of Aβ42, a key pathological hallmark of AD. We examine the molecular basis for stereochemistry-dependent inhibition of the formation of Aβ fibrils in vitro by a polyol, scyllo-inositol. We present molecular dynamics simulations of the monomeric, disordered aggregate, and protofibrillar states of Aβ(16-22), an amyloid-forming peptide fragment of full-length Aβ, successively with and without scyllo-inositol and its inactive stereoisomer chiro-inositol.

Ligand Binding / Docking (Cont'd)

Insights on the Binding of Thioflavin Derivative Markers to Amyloid-Like Fibril Models from Quantum Chemical Calculations

Jorge Alí-Torres, Albert Rimola, Cristina Rodríguez-Rodríguez, Luis Rodríguez-Santiago, and Mariona Sodupe [Universitat Autònoma de Barcelona]

J. Phys. Chem. B., **117**, 6674–6680, 2013**.**

Thioflavin-T (ThT) is one of the most widely used dyes for staining and identifying amyloid fibrils, which share a common parallel in register β-sheet structure. Unfortunately, ThT is a charged molecule, which limits its ability to cross the blood brain barrier and its use as an efficient dye for in vivo detection of amyloid fibrils. For this reason, several uncharged ThT derivatives have been designed and their binding properties to Aβ fibrils studied by fluorescence assays. The present contribution analyzes the binding of ThT (1) and neutral ThT derivatives (2–7) to a β-sheet model by means of quantum chemical B3LYP-D calculations and including solvent effects with the continuum CPCM method.

Enzyme Catalysis

Theoretical study on the proton shuttle mechanism of saccharopine dehydrogenase

Xiang Shenga, Jun Gaoa, Yongjun Liua [Shandong University], Chengbu Liua

J. Mol.Graph. and Mod., **42,** 17–25, 2013.

Saccharopine dehydrogenase (SDH) is the last enzyme in the AAA pathway of L-lysine biosynthesis. On the basis of crystal structures of SDH, the whole catalytic cycle of SDH has been studied by using density functional theory (DFT) method. Calculation results indicate that hydride transfer is the rate-limiting step with an energy barrier of 25.02 kcal/mol, and the overall catalytic reaction is calculated to be endothermic by 9.63 kcal/mol.

Quantum polarized ligand docking investigation to understand the significance of protonation states in histone deacetylase inhibitors

Subha Kalyaanamoorthya, Yi-Ping Phoebe Chena,

J. Mol.Graph. and Mod., **42,** 44–53, 2013.

The effects of different protonation states of the hydroxamic acid (HA) inhibitors against the class I histone deacetylase enzymes (HDACs) have been studied using the state of the art quantum polarized ligand docking (QPLD) and molecular mechanics-generalized Born surface area (MM-GBSA) approaches. The binding modes of the inhibitors and their inter-molecular interactions with class I HDACs, in response to the protonation states of the inhibitors, are explored. Our results indicate that the different protonation states of the inhibitors exhibit significant differences in their interactions with the catalytic zinc metal ion and the other active site residues in the HDAC enzymes, which in turn affect the 'Histidine-Aspartate' charge relay mechanism.

Enzyme Catalysis (Cont'd)

Investigation by MD simulation of the key residues related to substrate-binding and heme-release in human ferrochelatase

Yaxue Wang, Jingheng Wu, Jinqian Ju, Yong Shen[Sun Yat-sen University]

J. Mol.Mod., **19,** 2509-2518, 2013.

MD simulations of three models based on the crystal structure of the E343K variant of human ferrochelatase were performed in this study. The "open" and "closed" conformations of the enzyme obtained by simulations are in agreement with the corresponding crystal structures. The snapshots and the structure analysis indicate that alterations of the hydrogen bonds and the positions of E347 and E351 lead to a conformational change in the π-helix. The hydrogen bonded form of residue R164 could be regarded as a signal indicating alteration of the active site conformation.

Cation-Specific Effects on Enzymatic Catalysis Driven by Interactions at the Tunnel Mouth

Veronika Štěpánková, Jana Paterová, Jiří Damborský, Pavel Jungwirth, Radka Chaloupková, and Jan Heyda [,Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **117**, 6394–6402, 2013**.**

The self-assembly behavior of gemini (dimeric or twin-Cationic specificity which follows the Hofmeister series has been established for the catalytic efficiency of haloalkane dehalogenase LinB by a combination of molecular dynamics simulations and enzyme kinetic experiments. Simulations provided a detailed molecular picture of cation interactions with negatively charged residues on the protein surface, particularly at the tunnel mouth leading to the enzyme active site. On the basis of the binding affinities, cations were ordered as $Na^+ > K^+ > Rb^+ > Cs^+$. In agreement with this result, a steady-state kinetic analysis disclosed that the smaller alkali cations influence formation and productivity of enzyme–substrate complexes more efficiently than the larger ones.

Ab Initio QM/MM Calculations Show an Intersystem Crossing in the Hydrogen Abstraction Step in Dealkylation Catalyzed by AlkB

Dong Fang, Richard L. Lord, and G. Andrés Cisneros [Wayne State University]

J. Phys. Chem. B., **117**, 6410–6420, 2013**.**

AlkB is a bacterial enzyme that catalyzes the dealkylation of alkylated DNA bases. The rate-limiting step is known to be the abstraction of an H atom from the alkyl group on the damaged base by a FeIV-oxo species in the active site. We have used hybrid ab initioquantum mechanical/molecular mechanical methods to study this step in AlkB. Instead of forming an FeIII-oxyl radical from FeIV-oxo near the C–H activation transition state, the reactant is found to be an FeIII-oxyl with an intermediate-spin Fe (S = 3/2) ferromagnetically coupled to the oxyl radical, which we explore in detail using molecular orbital and quantum topological analyses.

Catalytic Mechanism of Angiotensin-Converting Enzyme and Effects of the Chloride Ion

Chunchun Zhang, Shanshan Wu, and Dingguo Xu [Sichuan University]

J. Phys. Chem. B., **117**, 6635–6645, 2013**.**

A!

The angiotensin-converting enzyme (ACE) exhibits critical functions in the conversion of angiotensin I to angiotensin II and the degradation of bradykinin and other vasoactive peptides. As a result, the ACE inhibition has become a promising approach in the treatment of hypertension, heart failure, and diabetic nephropathy. Extending our recent molecular dynamics simulation of the testis ACE in complex with a bona fide substrate molecule, hippuryl-histidyl-leucine, we presented here a detailed investigation of the hydrolytic process and possible influences of the chloride ion on the reaction using a combined QM/MM method.

Enzyme Catalysis (Cont'd)

Insights into the Catalytic Mechanism of Coral Allene Oxide Synthase: A Dispersion Corrected Density Functional Theory Study

Eric A. C. Bushnell, Rami Gherib, and James W. Gauld [University of Windsor]

J. Phys. Chem. B., **117**, 6701–6710, 2013**.**

In this present work the mechanism by which cAOS catalyzes the formation of allene oxide from its hydroperoxy substrate was computationally investigated by using a DFT-chemical cluster approach. In particular, the effects of dispersion interactions and DFT functional choice (M06, B3LYP, B3LYP*, and BP86), as well as the roles of multistate reactivity and the tyrosyl proximal ligand, were examined. It is observed that the computed relative free energies of stationary points along the overall pathway are sensitive to the choice of DFT functional, while the mechanism obtained is generally not.

Protein-Protein Interactions

Direct targeting of β-catenin: Inhibition of protein–protein interactions for the inactivation of Wnt signaling

Gernot Hahne, Tom N. Grossmann [Chemical Genomics Centre of the Max Planck Society]

Bioorg. and Med.Chem., **21**, 4020–4026, 2013.

The activation of developmental signaling pathways such as Notch, Hedgehog and Wnt has implications in the onset and progression of numerous types of cancer. Consequently, targeting of such pathways is considered an attractive therapeutic approach. Inhibition of the Wnt signaling cascade proves to be complicated, in part, due to the lack of druggable pathway components. The central hub in Wnt signaling is the protein β-catenin, which is involved in numerous protein–protein interactions.

Plucking the high hanging fruit: A systematic approach for targeting protein–protein interactions

Monika Raj, Brooke N. Bullock, Paramjit S. Arora [New York University]

Bioorg. and Med.Chem., **21**, 4051-4057 , 2013.

Development of specific ligands for protein targets that help decode the complexities of protein–protein interaction networks is a key goal for the field of chemical biology. Despite the emergence of powerful in silico and experimental high-throughput screening strategies, the discovery of synthetic ligands that selectively modulate protein–protein interactions remains a challenge for bioorganic and medicinal chemists. This Perspective discusses emerging principles for the rational design of PPI inhibitors.

Combined computational design of a zinc-binding site and a protein–protein interaction: One open zinc coordination site was not a robust hotspot for de novo ubiquitin binding

Bryan S. Der, Raamesh K. Jha, Steven M. Lewis, Peter M. Thompson, Gurkan Guntas and Brian Kuhlman[University of North Carolina at Chapel Hill]

Proteins: Stru. Fun. & Bioinf., **81**, 1245-1255, 2013.

We computationally designed a de novo protein–protein interaction between wild-type ubiquitin and a redesigned scaffold. Our strategy was to incorporate zinc at the designed interface to promote affinity and orientation specificity. A large set of monomeric scaffold surfaces were computationally engineered with three-residue zinc coordination sites, and the ubiquitin residue H68 was docked to the open coordination site to complete a tetrahedral zinc site. This single coordination bond was intended as a hotspot and polar interaction for ubiquitin binding, and surrounding residues on the scaffold were optimized primarily as hydrophobic residues using a rotamer-based sequence design protocol in Rosetta.

Membrane Proteins and Lipid Peptide Interactions

Cholesterol Translocation in a Phospholipid Membrane

Amit Choubey, Rajiv K. Kalia [University of Southern California], Noah Malmstadt, Aiichiro Nakano, Priya Vashishta

Biophysical Journal. **104**, 2429-2436, 2013.

Cholesterol (CHOL) molecules play a key role in modulating the rigidity of cell membranes and controlling intracellular transport and signal transduction. Using an all-atom molecular dynamics approach, we study the process of CHOL interleaflet transport (flip-flop) in a dipalmitoylphosphatidycholine (DPPC)-CHOL bilayer over a time period of 15 μs. We investigate the effect of the flip-flop process on mechanical stress across the bilayer and the role of CHOL in inducing molecular order in bilayer leaflets.

Development of the Knowledge-Based and Empirical Combined Scoring Algorithm (KECSA) To Score Protein–Ligand Interactions

Zheng Zheng and Kenneth M. Merz, Jr. [University of Florida]

J.Chem. Infor. and Mod. **53**, 1073–1083, 2013.

We describe a novel knowledge-based protein–ligand scoring function that employs a new definition for the reference state, allowing us to relate a statistical potential to a Lennard-Jones (LJ) potential. In this way, the LJ potential parameters were generated from protein–ligand complex structural data contained in the Protein Databank (PDB). Forty-nine (49) types of atomic pairwise interactions were derived using this method, which we call the knowledge-based and empirical combined scoring algorithm (KECSA). Two validation benchmarks were introduced to test the performance of KECSA.

Molecular Dynamics Simulations of Membrane–Sugar Interactions

Jon Kapla, Jakob Wohlert, Baltzar Stevensson, Olof Engström, Göran Widmalm, and Arnold Maliniak [Stockholm University]

J. Phys. Chem. B., **117**, 6667–6673, 2013**.**
A!

The self-assembly behavior of gemini (dimeric or twin-tail) dicarboxylate disodium surfactants is studied using molecular dynamics simulations. A united atom model is employed for the surfactants with fully atomistic counterions and water. This gemini architecture, in which two single tailed surfactants are joined through a flexible hydrophobic linker, has been shown to exhibit concentration-dependent aqueous self-assembly into lyotropic phases including hexagonal, gyroid, and lamellar morphologies. Our simulations reproduce the experimentally observed phases at similar amphiphile concentrations in water, including the unusual ability of these surfactants to form gyroid phases over unprecedentedly large amphiphile concentration windows.

Protein Folding

Using VIPT-Jump to Distinguish Between Different Folding Mechanisms: Application to BBL and a Trpzip

Chun-Wei Lin, Robert M. Culik, and Feng Gai [University of Pennsylvania,]

J. Am. Chem. Soc., 2013, **135**, 7668-7673

Protein folding involves a large number of sequential molecular steps or conformational substates. Thus, experimental characterization of the underlying folding energy landscape for any given protein is difficult. Herein, we present a new method that can be used to determine the major characteristics of the folding energy landscape in question, e.g., to distinguish between activated and barrierless downhill folding scenarios. This method is based on the idea that the conformational relaxation kinetics of different folding mechanisms at a given final condition will show different dependences on the initial condition.

New Insights into the Folding of a β-Sheet Miniprotein in a Reduced Space of Collective Hydrogen Bond Variables: Application to a Hydrodynamic Analysis of the Folding Flow

Igor V. Kalgin, Amedeo Caflisch, Sergei F. Chekmarev, and Martin Karplus [ISIS Université de Strasbourg,]

J. Phys. Chem. B., **117**, 6092–6105, 2013**.**
A!

A new analysis of the 20 μs equilibrium folding/unfolding molecular dynamics simulations of the three-stranded antiparallel β-sheet miniprotein (beta3s) in implicit solvent is presented. The conformation space is reduced in dimensionality by introduction of linear combinations of hydrogen bond distances as the collective variables making use of a specially adapted principal component analysis (PCA); i.e., to make structured conformations more pronounced, only the formed bonds are included in determining the principal components. It is shown that a three-dimensional (3D) subspace gives a meaningful representation of the folding behavior.

Molecular Mechanism of Misfolding and Aggregation of Aβ(13–23)

Sándor Lovas, Yuliang Zhang, Junping Yu, and Yuri L. Lyubchenko [University of Nebraska Medical Cente]

J. Phys. Chem. B., **117**, 6175–6186, 2013**.**

The misfolding and self-assembly of the amyloid-beta (Aβ) peptide into aggregates is a molecular signature of the development of Alzheimer's disease, but molecular mechanisms of the peptide aggregation remain unknown. Here, we combined Atomic Force Microscopy (AFM) and Molecular Dynamics (MD) simulations to characterize the misfolding process of an Aβ peptide. Dynamic force spectroscopy AFM analysis showed that the peptide forms stable dimers with a lifetime of 1 s. During MD simulations, isolated monomers gradually adopt essentially similar nonstructured conformations independent from the initial structure.

Protein Folding (Cont'd)

Overdamped Dynamics of Folded Protein Domains within a Locally Harmonic Basin Using Coarse Graining Based on a Partition of Compact Flexible Clusters

Anthony C. Manson and Rob D. Coalson [University of Pittsburgh]

J. Phys. Chem. B., **117**, 6646–6655, 2013**.**

A coarse-graining method based on the partitioning of atoms into compact flexible clusters is used to formulate the dynamics of the nonequilibrium response of a protein to ligand dissociation. The α-carbon positions are used as the degrees of freedom. The net stiffness between each pair of neighboring α-carbons is calculated for the quasi-static, overdamped regime within the harmonic (quadratic potential energy surface) using the equivalent stiffness matrix of the network of atoms occupying the intervening space within the locally interacting region. This localized approach realizes a divide and conquer strategy that results in a substantial reduction in computational complexity while accurately predicting relaxations under general loading conditions.

Folding and stability of helical bundle proteins from coarse-grained models

Abhijeet Kapoor [Iowa State University] and Alex Travesset

Proteins: Stru. Fun. & Bioinf., **81**, 1200–1211, 2013.
A!

We develop a coarse-grained model where solvent is considered implicitly, electrostatics are included as short-range interactions, and side-chains are coarse-grained to a single bead. The model depends on three main parameters: hydrophobic, electrostatic, and side-chain hydrogen bond strength. The parameters are determined by considering three level of approximations and characterizing the folding for three selected proteins (training set). Nine additional proteins (containing up to 126 residues) as well as mutated versions (test set) are folded with the given parameters.

Protein-Nucleic acid Interactions

Effect of Arginine-Rich Peptide Length on the Structure and Binding Strength of siRNA–Peptide Complexes

Minwoo Kim, Hyun Ryoung Kim, Su Young Chae, Ronald G. Larson, Hwankyu Lee [Dankook University], and Jae Chan Park

J. Phys. Chem. B., **117**, 6917–6926, 2013

Heparin decomplexation experiments, as well as all-atom (AA) and coarse-grained (CG) molecular dynamics (MD) simulations, were performed to determine the effect of the size of arginine(Arg)-rich peptides on the structure and binding strength of the siRNA–peptide complex. At a fixed peptide/siRNA mole ratio of 5:1 or 10:1, the siRNA complexes with peptides longer than nine Arg residues are more easily decomplexed by heparin than are those with nine Arg residues. At these mole ratios, peptides longer than nine Arg residues have cationic/anionic charge ratios in excess of unity, and produce more weakly bound complexes than nine Arg residue ones do.

Nucleic Acids

A tool for RNA sequencing sample identity check

Jinyan Huang, Jun Chen, Mark Lathrop, and Liming Liang[Harvard School of Public Health]

Bioinformatics. **29**, 1463-1464, 2013.

RNA sequencing data are becoming a major method of choice to study transcriptomes, including the mapping of gene expression quantitative trait loci (eQTLs). RNA sample contamination or swapping is a serious problem for downstream analysis and may result in false discovery and lose power to detect the true biological relationships. When genetic data are available, for example, in eQTL studies or samples have been previously genotyped or DNA sequenced, it is possible to combine genetic data and RNA-seq data to detect sample contamination and resolve sample swapping problems. In this article, we introduce a tool (IDCheck) that allows easy assessment of concordance between genotype and gene expression (RNA-seq) samples.

Partial Base Flipping Is Sufficient for Strand Slippage near DNA Duplex Termini

Nilesh K. Banavali [State University of New York at Albany]

J. Am. Chem. Soc., 2013, **135**, 8274-8282
A!

Strand slippage is a structural mechanism by which insertion–deletion (indel) mutations are introduced during replication by polymerases. Three-dimensional atomic-resolution structural pathways are still not known for the decades-old template slippage description. The dynamic nature of the process and the higher energy intermediates involved increase the difficulty of studying these processes experimentally. In the present study, restrained and unrestrained molecular dynamics simulations, carried out using multiple nucleic acid force fields, are used to demonstrate that partial base-flipping can be sufficient for strand slippage at DNA duplex termini.

Thermally Active Hybridization Drives the Crystallization of DNA-Functionalized Nanoparticles

Ting I. N. G. Li, Rastko Sknepnek, and Monica Olvera de la Cruz [Northwestern University,]

J. Am. Chem. Soc., 2013, **135**, 8535-8541

The selectivity of DNA recognition inspires an elegant protocol for designing versatile nanoparticle (NP) assemblies. We use molecular dynamics simulations to analyze dynamic aspects of the assembly process and identify ingredients that are key to a successful assembly of NP superlattices through DNA hybridization. A scale-accurate coarse-grained model faithfully captures the relevant contributions to the kinetics of the DNA hybridization process and is able to recover all experimentally reported to date binary superlattices (BCC, CsCl, AlB2, Cr3Si, and Cs6C60). We study the assembly mechanism in systems with up to 106degrees of freedom and find that the crystallization process is accompanied with a slight decrease of enthalpy.

Nucleic Acids (Cont'd)

MD simulations of HIV-1 RT primer–template complex: effect of modified nucleosides and antisense PNA oligomer

Mallikarjunachari V.N. Uppuladinne, Uddhavesh B. Sonavane & Rajendra R. Joshi [Pune University Campus]

J. Biomol. Stru. and Dyn., 31,(6) 539-560,2013.

Human immunodeficiency virus type 1 (HIV-1) requires the human $tRNA_3^{Lys}$ as a reverse transcriptase (RT) primer. The annealing of 3' terminal 18 nucleotides of $tRNA_3^{Lys}$ with the primer binding site (PBS) of viral RNA (vRNA) is crucial for reverse transcription. Additional contacts between the A rich (A-loop) region of vRNA and the anticodon domain of $tRNA_3^{Lys}$ are necessary, which show the specific requirement of $tRNA_3^{Lys}$. Molecular dynamics simulations have been carried out to study the effect of modified nucleosides on the vRNA–$tRNA_3^{Lys}$ complex stability and the destabilization effect of PNA oligomer on the vRNA–$tRNA_3^{Lys}$–PNA complex.

Exploration of the binding of DNA binding ligands to Staphylococcal DNA through QM/MM docking and molecular dynamics simulation

Periyasamy Vijayalakshmi, Chandrabose Selvaraj,Sanjeev Kumar Singh, Jaganathan Nisha, Kandasamy Saipriya & Pitchai Daisy[Bioinformatics centre (BIF), Tiruchirapalli]

J. Biomol. Stru. and Dyn., 31,(6) 561-571,2013.

DNA binding ligands (DBL) were reported to bind the minor groove of bacterial DNA. In the present study, DBL were analyzed and screened for their *Staphylococcus* inhibitory activity by inhibiting the *Staphylococcal* DNA replication. The orientation and the ligand-receptor interactions of DBL within the DNA-binding pocket were investigated applying a multi-step docking protocol using Glide and QM/MM docking. The polarization of ligands with QM/MM for DNA-ligand docking with *Staphylococcal* DNA minor groove was performed in order to understand their possible interactions.

DNA Bending Propensity in the Presence of Base Mismatches: Implications for DNA Repair

Monika Sharma, Alexander V. Predeus, Shayantani Mukherjee, and Michael Feig [Michigan State University]

J. Phys. Chem. B., **117**, 6194–6205, 2013**.**
A!

DNA bending is believed to facilitate the initial recognition of the mismatched base for repair. The repair efficiencies are dependent on both the mismatch type and neighboring nucleotide sequence. We have studied bending of several DNA duplexes containing canonical matches: A:T and G:C; various mismatches: A:A, A:C, G:A, G:G, G:T, C:C, C:T, and T:T; and a bis-abasic site: X:X. Free-energy profiles were generated for DNA bending using umbrella sampling. The highest energetic cost associated with DNA bending is observed for canonical matches while bending free energies are lower in the presence of mismatches, with the lowest value for the abasic site.

Surfaces, Catalysts, and Materials Subjects

Computer Simulation–Molecular-Thermodynamic Framework to Predict the Micellization Behavior of Mixtures of Surfactants: Application to Binary Surfactant Mixtures

Jaisree Iyer, Jonathan D. Mendenhall, and Daniel Blankschtein [Massachusetts Institute of Technology]

J. Phys. Chem. B., **117**, 6430–6442, 2013**.**

We present a computer simulation–molecular-thermodynamic (CSMT) framework to model the micellization behavior of mixtures of surfactants in which hydration information from all-atomistic simulations of surfactant mixed micelles and monomers in aqueous solution is incorporated into a well-established molecular-thermodynamic framework for mixed surfactant micellization. In addition, we address the challenges associated with the practical implementation of the CSMT framework by formulating a simpler mixture CSMT model based on a composition-weighted average approach involving single-component micelle simulations of the mixture constituents.

Investigation of the Bulk Modulus of Silica Aerogel Using Molecular Dynamics Simulations of a Coarse-Grained Model

Carlos A. Ferreiro-Rangel and Lev D. Gelb [University of Texas at Dallas]

J. Phys. Chem. B., **117**, 7095–7105, 2013**.**

Structural and mechanical properties of silica aerogels are studied using a flexible coarse-grained model and a variety of simulation techniques. The model, introduced in a previous study (J. Phys. Chem. C 2007, 111, 15792−15802), consists of spherical "primary" gel particles that interact through weak nonbonded forces and through microscopically motivated interparticle bonds that may break and form during the simulations. Aerogel models are prepared using a three-stage protocol consisting of separate simulations of gelation, aging, and a final relaxation during which no further bond formation is permitted. Models of varying particle size, density, and size dispersity are considered.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Similarity Boosted Quantitative Structure–Activity Relationship—A Systematic Study of Enhancing Structural Descriptors by Molecular Similarity

Tobias Girschick, Pedro R. Almeida, Stefan Kramer [Johannes Gutenberg-Universität Mainz], and Jonna Stålring

J.Chem. Infor. and Mod. **53**, 1017–1025, 2013.

The concept of molecular similarity is one of the most central in the fields of predictive toxicology and quantitative structure–activity relationship (QSAR) research. Many toxicological responses result from a multimechanistic process and, consequently, structural diversity among the active compounds is likely. Combining this knowledge, we introduce similarity boosted QSAR modeling, where we calculate molecular descriptors using similarities with respect to representative reference compounds to aid a statistical learning algorithm in distinguishing between different structural classes.

Potentials and Parameters

A partition function-based weighting scheme in force field parameter development using ab initio calculation results in global configurational space

Yao Wu ,Xiaodong Dai ,Niu Huang [Zhongguancun Life Science Park, Beijing] ,Lifeng Zhao

J. Comp. Chem., **34**, 1271–1282, 2013.

In force field parameter development using ab initio potential energy surfaces (PES) as target data, an important but often neglected matter is the lack of a weighting scheme with optimal discrimination power to fit the target data. Here, we developed a novel partition function-based weighting scheme, which not only fits the target potential energies exponentially like the general Boltzmann weighting method, but also reduces the effect of fitting errors leading to overfitting.

Parameters for Molecular Dynamics Simulations of Manganese-Containing Metalloproteins

Rui P. P. Neves, Sérgio F. Sousa, Pedro A. Fernandes, and Maria J. Ramos [Universidade do Porto]

J. Chem. Theor. and Comp, **9**, 2718-2732, 2013.

A set of geometrical parameters has been determined for single manganese metalloproteins for the AMBER force field, and ultimately to other force fields with a similar philosophy. Twelve (12) models from 9 different single-cluster manganese proteins were optimized and parametrized, using a bonded model approach. Mn-ligand bonds, Mn-ligand angles, and Restrained Electrostatic Potential charges for all the 74 residues in the first metal coordination sphere of each Mn metalloprotein were parametrized. The determined parameters were validated with molecular dynamics simulations and several statistics strategies were used to analyze the results.

Solvation Energy

Comparative assessment of computational methods for the determination of solvation free energies in alcohol-based molecules

Silvia A. Martins, Sergio F. Sousa[Universidade do Porto]

J. Comp. Chem., **34**, 1354–1362, 2013.

The determination of differences in solvation free energies between related drug molecules remains an important challenge in computational drug optimization, when fast and accurate calculation of differences in binding free energy are required. In this study, we have evaluated the performance of five commonly used polarized continuum model (PCM) methodologies in the determination of solvation free energies for 53 typical alcohol and alkane small molecules.

Molecular Dynamics

Calcium Causes a Conformational Change in Lamin A Tail Domain that Promotes Farnesyl-Mediated Membrane Association

Agnieszka Kalinowski, Zhao Qin, Kelli Coffey, Ravi Kodali, Markus J. Buehler, Mathias Lösche, Kris Noel Dahl [Carnegie Mellon University]

Biophysical Journal. **104**, 2246-2253, 2013.

A!

Lamin proteins contribute to nuclear structure and function, primarily at the inner nuclear membrane. The posttranslational processing pathway of lamin A includes farnesylation of the C-terminus, likely to increase membrane association, and subsequent proteolytic cleavage of the C-terminus. Hutchinson Gilford progeria syndrome is a premature aging disorder wherein a mutant version of lamin A, Δ50 lamin A, retains its farnesylation. We report here that membrane association of farnesylated Δ50 lamin A tail domains requires calcium. Experimental evidence and molecular dynamics simulations collectively suggest that the farnesyl group is sequestered within a hydrophobic region in the tail domain in the absence of calcium.

The Mechanism of Na^+/K^+ Selectivity in Mammalian Voltage-Gated Sodium Channels Based on Molecular Dynamics Simulation

Mengdie Xia, Huihui Liu, Yang Li, Nieng Yan, Haipeng Gong [Tsinghua University,]

Biophysical Journal. **104**, 2401-2409, 2013.

A!

Voltage-gated sodium (Na_v) channels and their Na^+/K^+ selectivity are of great importance in the mammalian neuronal signaling. According to mutational analysis, the Na^+/K^+ selectivity in mammalian Na_v channels is mainly determined by the Lys and Asp/Glu residues located at the constriction site within the selectivity filter. Despite successful molecular dynamics simulations conducted on the prokaryotic Na_v channels, the lack of Lys at the constriction site of prokaryotic Na_v channels limits how much can be learned about the Na^+/K^+ selectivity in mammalian Na_v channels. In this work, we modeled the mammalian Na_v channel by mutating the key residues at the constriction site in a prokaryotic Na_v channel (Na_vRh) to its mammalian counterpart.

The effect of Zn2+ on Pelodiscus sinensis creatine kinase: unfolding and aggregation studies

Su-Fang Wang, Jinhyuk Lee, Wei Wang, Yue-Xiu Si, Caiyan Li, Tae-Rae Kim, Jun-Mo Yang, Shang-Jun Yin & Guo-Ying Qian[Zhejiang Wanli University]

J. Biomol. Stru. and Dyn., 31,(6) 572-590,2013.

A!

We studied the effects of Zn^{2+} on creatine kinase from the Chinese soft-shelled turtle, *Pelodiscus sinensis* (PSCK). Zn^{2+} inactivated the activity of PSCK ($IC_{50} = .079 \pm .004$ mM) following first-order kinetics consistent with multiple phases. The spectrofluorimetry results showed that Zn^{2+} induced significant tertiary structural changes of PSCK with exposure to hydrophobic surfaces and that Zn^{2+} directly induced PSCK aggregation. The addition of osmolytes such as glycine, proline, and liquaemin successfully blocked PSCK aggregation, recovering the conformation and activity of PSCK. We measured the ORF gene sequence of PSCK by rapid amplification of cDNA end and simulated the 3D structure of PSCK.

Molecular Dynamics (Cont'd)

Matching of Additive and Polarizable Force Fields for Multiscale Condensed Phase Simulations

Christopher M. Baker and Robert B. Best [University of Cambridge,]

J. Chem. Theor. and Comp, **9**, 2826-2837, 2013.

Inclusion of electronic polarization effects is one of the key aspects in which the accuracy of current biomolecular force fields may be improved. The principal drawback of such approaches is the computational cost, which typically ranges from 3 to 10 times that of the equivalent additive model, and may be greater for more sophisticated treatments of polarization or other many-body effects. Here, we present a multiscale approach that may be used to enhance the sampling in simulations with polarizable models, by using the additive model as a tool to explore configuration space.

Induced Dipoles Incorporated into All-Atom Zn Protein Simulations with Multiscale Modeling

Yan-Dong Huang and Jian-Wei Shuai [Xiamen University]

J. Phys. Chem. B., **117**, 6138–6148, 2013**.**
A!

Zinc is found saturated in the deposited Amyloid-beta (Aβ) peptide plaques in Alzheimer's disease (AD) patients' brains. Binding of zinc promotes aggregation of Aβ, including the pathogenic aggregates. Up to now, only the region 1–16 of Aβ complexed with zinc (Aβ1–16–Zn) is defined structurally in experiment. In order to explore the induced polarization effect of zinc on the global fluctuations and the experimentally observed coordination mode of Aβ1–16–Zn, we consider an all-atom molecular dynamics (MD) of Aβ1–16–Zn solvated in implicit water.

QM and QM/MM

Quantum Mechanics/Molecular Mechanics Modeling of Regioselectivity of Drug Metabolism in Cytochrome P450 2C9

Richard Lonsdale, Kerensa T. Houghton, Jolanta Żurek, Christine M. Bathelt, Nicolas Foloppe, Marcel J. de Groot, Jeremy N. Harvey, and Adrian J. Mulholland [University of Bristol]

J. Am. Chem. Soc., 2013, **135**, 8001-8015
A!

Cytochrome P450 enzymes (P450s) are important in drug metabolism and have been linked to adverse drug reactions. P450s display broad substrate reactivity, and prediction of metabolites is complex. QM/MM studies of P450 reactivity have provided insight into important details of the reaction mechanisms and have the potential to make predictions of metabolite formation. Here we present a comprehensive study of the oxidation of three widely used pharmaceutical compounds (S-ibuprofen, diclofenac, and S-warfarin) by one of the major drug-metabolizing P450 isoforms, CYP2C9. The reaction barriers to substrate oxidation by the iron-oxo species (Compound I) have been calculated at the B3LYP-D/CHARMM27 level for different possible metabolism sites for each drug, on multiple pathways.

QM and QM/MM (Cont'd)

Modeling of phytochrome absorption spectra

Olle Falklöf, Bo Durbeej [Linköping University,]

J. Comp. Chem., **34**, 1363–1374, 2013.

Phytochromes constitute one of the six well-characterized families of photosensory proteins in Nature. From the viewpoint of computational modeling, however, phytochromes have been the subject of much fewer studies than most other families of photosensory proteins, which is likely a consequence of relevant high-resolution structural data becoming available only in recent years. In this work, hybrid quantum mechanics/molecular mechanics (QM/MM) methods are used to calculate UV-vis absorption spectra of Deinococcus radiodurans bacteriophytochrome.

MD and QM/MM study on catalytic mechanism of a FAD-dependent enzyme ORF36: For nitro sugar biosynthesis

Yanwei Li, Lei Ding, Qingzhu Zhang [Shandong University] , Wenxing Wang

J. Mol.Graph. and Mod., **42,** 9–16, 2013.
A!

The catalytic mechanism of a FAD-dependent nitrososynthase (ORF36) was studied with molecular dynamics (MD) and quantum mechanical/molecular mechanical (QM/MM) methods. Residues Leu160 and Phe374 play an important role during the FAD binding with ORF36. Similar phenylalanine/leucine pair was found in the other two enzymes of this family. For the second oxidation step of ORF36 toward thymidine diphosphate-L-epi-vancosamine, three elementary catalytic steps were found: a hydroxylation step, a hydrogen back-transfer step and a hydroxyl group elimination step.

Comparative studies for evaluation of CO2fixation in the cavity of the Rubisco enzyme using QM, QM/MM and linear-scaling DFT methods

Morad M. El-Hendawy, Niall J. English, Damian A. Mooney[University College Dublin]

J. Mol.Mod., **19,** 2329-2334, 2013.

We evaluate the minimum energy configuration (MM) and binding free energy (QM/MM and QM) of CO2 to Rubisco, of fundamental importance to the carboxylation step of the reaction. Two structural motifs have been used to achieve this goal, one of which starts from the initial X-ray Protein Data Bank structure of Rubisco's active centre (671 atoms), and the other is a simplified, smaller model (77 atoms) which has been used most successfully, thus far, for study.

Structure of dipeptides having N-terminal selenocysteine residues: a DFT study in gas and aqueous phase

Shilpi Mandal, Gunajyoti Das [North Eastern Hill University]

J. Mol.Mod., **19,** 2613-2623, 2013.

Over the last few decades, dipeptides as well as their analogues have served as important model systems for the computational studies concerning the structure of protein and energetics of protein folding. Here, we present a density functional structural study on a set of seven dipeptides having N-terminal selenocysteine residues (the component in the C-terminus is varied with seven different combinations viz. Ala, Phe, Glu, Thr, Asn, Arg and Sec) in gas and simulated aqueous phase using a polarizable continuum model (PCM).

QM and QM/MM (Cont'd)

Direct Absolute pKa Predictions and Proton Transfer Mechanisms of Small Molecules in Aqueous Solution by QM/MM-MD

Nizam Uddin, Tae Hoon Choi, and Cheol Ho Choi [Kyungpook National University]

J. Phys. Chem. B., **117**, 6269–6275, 2013**.**

The pKa values of HF, HCOOH, CH3COOH, CH3CH2COOH, H2CO3, HOCl, NH4+, CH3NH3+, H2O2, and CH3CH2OH in aqueous solution were predicted by QM/MM-MD in combination with umbrella samplings adopting the flexible asymmetric coordinate (FAC). This unique combination yielded remarkably accurate values with the maximum and root-mean-square errors of 0.45 and 0.22 in pKa units, respectively, without any numerical or experimental adjustments. The stability of the initially formed Coulomb pair rather than the proton transfer stage turned out to be the rate-determining step, implying that the stabilizations of the created ions require a large free energy increase.

Sum-Frequency-Generation Vibration Spectroscopy and Density Functional Theory Calculations with Dispersion Corrections (DFT-D2) for Cellulose Iα and Iβ

Christopher M. Lee, Naseer M. A. Mohamed, Heath D. Watts, James D. Kubicki, and Seong H. Kim [The Pennsylvania State University]

J. Phys. Chem. B., **117**, 6681–6692, 2013**.**

Sum-frequency-generation (SFG) vibration spectroscopy selectively detects noncentrosymmetric vibrational modes in crystalline cellulose inside intact lignocellulose. However, SFG peak assignment in biomass samples is challenging due to the complexity of the SFG processes and the lack of reference SFG spectra from the two crystal forms synthesized in nature, cellulose Iα and Iβ. This paper compares SFG spectra of laterally aligned cellulose Iα and Iβ crystals with vibration frequencies calculated from density functional theory with dispersion corrections (DFT-D2).

Comparative or Homology Modeling

Optimized Method of G-Protein-Coupled Receptor Homology Modeling: Its Application to the Discovery of Novel CXCR7 Ligands

Yasushi Yoshikawa, Shinya Oishi, Tatsuhiko Kubo, Noriko Tanahara, Nobutaka Fujii, and Toshio Furuya [Research & Development Division, Tokyo]

J.Med.Chem., **56,** 4236–4251, 2013.

Homology modeling of G-protein-coupled seven-transmembrane receptors (GPCRs) remains a challenge despite the increasing number of released GPCR crystal structures. This challenge can be attributed to the low sequence identity and structural diversity of the ligand-binding pocket of GPCRs. We have developed an optimized GPCR structure modeling method based on multiple GPCR crystal structures. This method was designed to be applicable to distantly related receptors of known structural templates.

Ligand Docking

Fighting Obesity with a Sugar-Based Library: Discovery of Novel MCH-1R Antagonists by a New Computational–VAST Approach for Exploration of GPCR Binding Sites

Alexander Heifetz [Oxfordshire], Oliver Barker, Geraldine Verquin, Norbert Wimmer, Wim Meutermans, Sandeep Pal, Richard J. Law, and Mark Whittaker

J.Chem. Infor. and Mod. **53**, 1084–1099, 2013.

Obesity is an increasingly common disease. While antagonism of the melanin-concentrating hormone-1 receptor (MCH-1R) has been widely reported as a promising therapeutic avenue for obesity treatment, no MCH-1R antagonists have reached the market. Discovery and optimization of new chemical matter targeting MCH-1R is hindered by reduced HTS success rates and a lack of structural information about the MCH-1R binding site. We present here a conceptually pioneering approach that integrates GPCR modeling with design, synthesis, and screening of a diverse library of sugar-based compounds from the VAST technology (versatile assembly on stable templates) to provide structural insights on the MCH-1R binding site.

Identification of a New Binding Site in E. coli FabH using Molecular Dynamics Simulations: Validation by Computational Alanine Mutagenesis and Docking Studies

Divya Ramamoorthy, Edward Turos, and Wayne C. Guida [University of South Florida]

J.Chem. Infor. and Mod. **53**, 1138–1156, 2013.
S !

FabH (Fatty acid biosynthesis, enzyme H, also referred to as β-ketoacyl-ACP-synthase III) is a key condensing enzyme in the type II fatty acid synthesis (FAS) system. The FAS pathway in bacteria is essential for growth and survival and vastly differs from the human FAS pathway. Enzymes involved in this pathway have arisen as promising biomolecular targets for discovery of new antibacterial drugs. The aim of this study was to elucidate structural details of the dimer interface region by means of computational modeling, including molecular dynamics (MD) simulations, in order to derive information for the structure-based design of new FabH inhibitors.

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3. J O U R N A L R E V I E W S

Journal of Computational Chemistry, 34 (15), June, 2013.

1271–1282 **A partition function-based weighting scheme in force field parameter development using ab initio calculation results in global configurational space** Yao Wu ,Xiaodong Dai ,Niu Huang [Zhongguancun Life Science Park, Beijing] ,Lifeng Zhao

See Methodology / Potentilas and Parameters.

1283–1290 **Simulation of mesogenic diruthenium tetracarboxylates: Development of a force field for coordination polymers of the MMX type** Maria Ana Castro ,Adrian E. Roitberg[University of Florida] Fabio D. Cukiernik

A classical molecular mechanics force field, able to simulate coordination polymers (CP) based on ruthenium carboxylates (Ru2(O2CReq)4Lax) (eq = equatorial group containing aliphatic chains, Lax= axial ligand), has been developed. New parameters extracted from experimental data and quantum calculations on short aliphatic chains model systems were included in the generalized AMBER force field.

1291–1310 **Search of truncation of (N−1) electron basis containing full connected triple excitations in computing main and satellite ionization potentials via fock-space coupled cluster approach** Kalipada Adhikari, Sudip Chattopadhyay,Barin Kumar De, Amitava Sharma,Ranendu Kumar Nath, Dhiman Sinha [Tripura University, Suryamaninagar,]

A valence-universal multireference coupled cluster (VUMRCC) theory, realized via the eigenvalue independent partitioning (EIP) route, has been implemented with full inclusion of triples excitations for computing and analyzing the entire main and several satellite peaks in the ionization potential spectra of several molecules.

1311–1320 **Local hartree–fock orbitals using a three-level optimization strategy for the energy** Ida-Marie Høyvik [Aarhus University,]Branislav Jansik,Kasper Kristensen ,Poul Jørgensen,

Using the three-level energy optimization procedure combined with a refined version of the least-change strategy for the orbitals—where an explicit localization is performed at the valence basis level—it is shown how to more efficiently determine a set of local Hartree–Fock orbitals.

1321–1331 **Pseudosymmetry analysis of molecular orbitals** David Casanova [Universitat de Barcelona,] Pere Alemany,Andrés Falceto ,Abel Carreras ,Santiago Alvarez

We introduce a pseudosymmetry analysis of molecular orbitals by means of the newly proposed irreducible representation measures. We develop a general algorithm to quantify the pseudosymmetry content of a given object within the framework of the finite group algebra.

1332–1340 **Combination of COSMOmic and molecular dynamics simulations for the calculation of membrane-water partition coefficients** Sven Jakobtorweihen [Hamburg University of Technology] Thomas Ingram ,Irina Smirnova

See Methodology / Solvation Energy.

1341–1353 **Which density functional is close to CCSD accuracy to describe geometry and interaction energy of small non-covalent dimers? A benchmark study using gaussian09** Karunakaran Remya, Cherumuttathu H. Suresh[CSIR-National Institute for Interdisciplinary,]

A benchmark study on all possible density functional theory (DFT) methods in Gaussian09 is done to locate functionals that agree well with CCSD/aug-cc-pVTZ geometry and Ave-CCSD(T)/(Q-T) interaction energy (Eint) for small non-covalently interacting molecular dimers in "dispersion-dominated" (class 1), "dipole-induced dipole" (class 2), and "dipole-dipole" (class 3) classes.

1354–1362 **Comparative assessment of computational methods for the determination of solvation free energies in alcohol-based molecules** Silvia A. Martins ,Sergio F. Sousa[Universidade do Porto]

See Methodology / Solvation Free Energy.

Journal of Computational Chemistry, 34 (16), June, 2013.

1363–1374 **Modeling of phytochrome absorption spectra** Olle Falklöf, Bo Durbeej [Linköping University,]

See Methodology / QM and QM/MM.

1375–1384 **On-the-fly reconstruction of free-energy profiles using logarithmic mean-force dynamics** Tetsuya Morishita [National Institute of Advanced Industrial Science and Technology (AIST), Ibaraki] Satoru G. Itoh ,Hisashi Okumura ,Masuhiro Mikami

Mean-force dynamics (MFD), which is a fictitious dynamics for a set of collective variables on a potential of mean-force, is a powerful algorithm to efficiently explore free-energy landscapes. Recently, we have introduced logarithmic MFD (LogMFD) (Morishita et al., Phys. Rev. E 2012, 85, 066702) which overcomes difficulties encounterd in free-energy calculations using standard approaches such as thermodynamic integration.

Journal of Computational Chemistry, 34 (17), June, 2013.

1439–1445 **Photodeactivation paths in norbornadiene** Ivana Antol [Rudjer Bošković Institute, Zagreb]

The first high level ab initio quantum-chemical calculations of potential energy surfaces (PESs) for low-lying singlet excited states of norbornadiene in the gas phase are presented. The optimization of the stationary points (minima and conical intersections) and the recalculation of the energies were performed using the multireference configuration interaction with singles (MR-CIS) and the multiconfigurational second-order perturbation (CASPT2) methods, respectively.

1446–1455 **On the Vibrational linear and nonlinear optical properties of compounds involving noble gas atoms: HXeOXeH, HXeOXeF, and FXeOXeF**Aggelos Avramopoulos[National Hellenic Research Foundation, Athen], Heribert Reis,Josep M. Luis, Manthos G. Papadopoulos

The vibrational (hyper)polarizabilities of some selected Xe derivatives are studied in the context of Bishop–Kirtman perturbation theory (BKPT) and numerical finite field methodology. It was found that for this set of rare gas compounds, the static vibrational properties are quite large, in comparison to the corresponding electronic ones, especially those of the second hyperpolarizability.

1456–1462 **Pipek–Mezey localization of occupied and virtual orbitals**Ida-Marie H∅yvik [Aarhus University,] ,Branislav Jansik ,Poul J∅rgensen

Recent advances in orbital localization algorithms are used to minimize the Pipek–Mezey localization function for both occupied and virtual Hartree–Fock orbitals. Virtual Pipek–Mezey orbitals for large molecular systems have previously not been considered in the literature. For this work, the Pipek–Mezey (PM) localization function is implemented for both the Mulliken and a Löwdin population analysis.

1463–1475 **Modeling peptide binding to anionic membrane pores**Yi He, Lidia Prieto , Themis Lazaridis[City College of New York]

See Applications / Ligand Binding.

1476–1485 **Use of ab initio methods for the interpretation of the experimental IR reflectance spectra of crystalline compounds**Marco De La Pierre [Università di Torino, Via P. Giuria 7],Cédric Carteret,Roberto Orlando, Roberto Dovesi

It is shown that ab initio simulation can be used as a powerful complementary tool in the interpretation of the experimental reflectance spectra R(ν) of crystalline compounds. Experimental frequencies and intensities are obtained from a best fit of R(ν) with a set of damped harmonic oscillators, whose number and initial position in frequency can dramatically influence the final results, as the parameters are strongly correlated.

1486–1496 **Attractive electron–electron interactions within robust local fitting approximations** Patrick Merlot,Thomas Kjærgaard,Trygve Helgaker,Roland Lindh,Francesco Aquilante, Simen Reine1,Thomas Bondo Pedersen[University of Oslo]

An analysis of Dunlap's robust fitting approach reveals that the resulting two-electron integral matrix is not manifestly positive semidefinite when local fitting domains or non-Coulomb fitting metrics are used. We present a highly local approximate method for evaluating four-center two-electron integrals based on the

resolution-of-the-identity (RI) approximation and apply it to the construction of the Coulomb and exchange contributions to the Fock matrix.

1497–1507 **Finding optimal finite field strengths allowing for a maximum of precision in the calculation of polarizabilities and hyperpolarizabilities** Ahmed A. K. Mohammed,Peter A. Limacher [University of Namur]Benoît Champagne

The finite field method, widely used for the calculation of static dipole polarizabilities or the first and second hyperpolarizabilities of molecules and polymers, is thoroughly explored. The application of different field strengths and the impact on the precision of the calculations were investigated.

1508–1526 **Program fullerene—a software package for constructing and analyzing structures of regular fullerenes** Peter Schwerdtfeger [Massey University Auckland], Lukas Wirz ,James Avery

Fullerene (Version 4.4) is a general purpose open-source program that can generate any fullerene isomer, perform topological and graph theoretical analysis, as well as calculate a number of physical and chemical properties. The program creates symmetric planar drawings of the fullerene graph and generates accurate molecular 3D geometries by way of force-field optimization, serving as a good starting point for further quantum theoretical treatments.

Journal of Molecular Modeling, 19(6), June, 2013.

2183-2188 **Trivalent cations switch the selectivity in nanopores** Alberto G. Albesa [Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA, Argentina] Matías Rafti, José L. Vicente

In this letter, we study the effect of cation charge on anion selectivity in the pore using grand canonical Monte Carlo simulations.

2189-2195 **Theoretical study on rate constants for the reactions of CF3CH2NH2 (TFEA) with the hydroxyl radical at 298 K and atmospheric pressure** Bhupesh Kumar Mishra, Arup Kumar Chakrabartty, Ramesh Chandra Deka[Tezpur University]

Theoretical investigations are carried out on reaction mechanism of the reactions of CF3CH2NH2(TFEA) with the OH radical by means of ab initio and DFT methods. The electronic structure information on the potential energy surface for each reaction is obtained at MPWB1K/6-31+G(d,p) level and energetic information is further refined by calculating the energy of the species with a Gaussian-2 method, G2(MP2).

2197-2203 **Sensing behavior of Al-rich AlN nanotube toward hydrogen cyanide** Javad Beheshtian, Ali Ahmadi Peyghan [Islamic Azad University], Zargham Bagheri

In order to explore a sensor for detection of toxic hydrogen cyanide (HCN) molecules, interaction of pristine and defected Al-rich aluminum nitride nanotubes (AlNNT) with a HCN molecule has been investigated using density functional theory calculations in terms of energetic, geometric, and electronic properties.

Gln/Tyr distal iron coordination, adaptation to extreme environmental conditions, and lack of a D helix suggests that ligand migration in HGbI differs from other previously studied globins.

2273-2283 **Optical properties of GaAs nanocrystals: influence of an electric field**Masoud Bezi Javan [Golestan University]

A study of the electronic and optical properties of the hydrogen-terminated GaAs nanocrystals Ga68As68H96 and Ga92As80H108 is presented. In this study, their dielectric functions, refractive indices, and absorption coefficients were calculated using density functional theory (DFT). The influence of a uniform external electric field on the optical properties of the nanocrystals was also explored.

2285-2298 **A DFT method for the study of the antioxidant action mechanism of resveratrol derivatives** Ali Benayahoum, Habiba Amira-Guebailia [Guelma University], Omar Houache

Quantum-chemical calculations using DFT, have been performed to explain the molecular structure antioxidant activity relationship of resveratrol (RSV) (1) analogues: 3,4-dihydroxy-trans-stilbene (3,4-DHS) (2); 4,4′-dihydroxy-trans-stilbene (4,4′-DHS) (3); 4-hydroxy-trans-stilbene (4-HS) (4); 3,5-dihydroxy-trans-stilbene (3,5-DHS) (5); 3,3′-dimethoxy-4,4′-dihydroxy-trans-stilbene (3,3′-DM-4,4′-DHS) (6); 2,4-dihydroxy-trans-stilbene (2,4-DHS) (7) and 2,4,4′-trihydroxy-trans-stilbene (2,4,4′-THS) (8).

2299-2308 **Excited-state relaxation paths of oxo/hydroxy and N9H/N7H tautomers of guanine: a CC2 theoretical study**Vassil B. Delchev[University of Plovdiv, Tzar Assen]

We performed a theoretical investigation, at the CC2/aug-cc-pVDZ level, of the ring-deformation mechanisms of four guanine tautomers (oxo, hydroxy, N9H, and N7H). The study showed that the optimized conical intersections S0/S1 are accessible through the $1\pi\pi^*$ excited states of tautomers.

2309-2315 **Density functional studies of the stepwise substitution of pyrrole, furan, and thiophene with BCO** Xiao-Fang Qin [Ludong University, Yantai], Feng Wang, Hai-Shun Wu

The structures, stabilities, and aromaticities of a series of (BCO) n (CH)4–n NH (n = 0–4), (BCO) n(CH)4–n O (n = 0–4), and (BCO) n (CH)4–n S (n = 0–4) clusters were investigated at the B3LYP density functional level of theory. The most stable positional isomers of the individual clusters were obtained. All of the calculated CO binding energies were exothermic, suggesting that these BCO-substituted species are stable.

2317-2327 **A computational approach to design energetic ionic liquids** Hari Ji Singh [DDU Gorakhpur University], Uttama Mukherjee

The present work deals with the theoretical estimation of ion-pair binding energies and the energetic properties of four ion pairs formed by combining the 1-butyl-2,4-dinitro-3-methyl imidazolium ion with nitrate (I), perchlorate (II), dinitramide (III), or 3,5-dinitro-1,2,4-triazolate (IV) anions.

2329-2334 **Comparative studies for evaluation of CO2fixation in the cavity of the Rubisco enzyme using QM, QM/MM and linear-scaling DFT methods** Morad M. El-Hendawy, Niall J. English, Damian A. Mooney[University College Dublin]

See Methodology / QM and QM/MM.

2335-234 **First-principles simulations of the chemical functionalization of (5,5) boron nitride nanotubes** Ernesto Chigo Anota [Ciudad Universitaria, San Manuel], Gregorio H. Cocoletzi

We perform density functional theory studies to investigate structural and electronic properties of the (5,5) boron nitride nanotubes (BNNTs) with surfaces and ends functionalized by thiol (SH) and hydroxyl (OH) groups.

2343-2353 **Stabilization of gold nanowires inside nanoaggregates of cyclo[8]thiophene, cyclo[8]selenophene, and cyclo[8]tellurophene: a theoretical study**Xiaomin Huang, Serguei Fomine [Universidad Nacional Autónoma de México]

The stabilities and electronic properties of gold clusters containing up to six atoms trapped inside cyclo[8]thiophene (CS8), cyclo[8]selenophene (CSe8), and cyclo[8]tellurophene (CTe8) nanoaggregates have been studied using the M06 functional.

2355-2361 **Assessing the accuracy of the general AMBER force field for 2,2,2-trifluoroethanol as solvent**Xiangyu Jia, John Z.H. Zhang, Ye Mei[East China Normal University]

The alcohol-based cosolvent 2,2,2-trifluoroethanol (TFE) has been used widely in protein science and engineering. Many experimental and computational studies of its impact on protein structure have been carried out, but consensus on the mechanism has not been reached. In the past decade, several molecular mechanical models have been proposed to model the structure and dynamics of TFE.

2363-2373 **Parametrization scheme with accuracy and transferability for tight-binding electronic structure calculations with extended Hückel approximation and molecular dynamics simulations** Shinya Nishino [**The University of Tokyo]**, Takeo Fujiwara

A transferable tight-binding parametrization procedure for extended Hückel approximation is proposed, with the charge self-consistent scheme, that could be applied to the quantum molecular dynamics (MD) simulation for long-time dynamics of large-scale systems.

2375-2382 **A comparative study on carbon, boron-nitride, boron-phosphide and silicon-carbide nanotubes based on surface electrostatic potentials and average local ionization energies** Mehdi D. Esrafili, Hadi Behzadi[University of Maragheh]

A density functional theory study was carried out to predict the electrostatic potentials as well as average local ionization energies on both the outer and the inner surfaces of carbon, boron-nitride (BN), boron-phosphide (BP) and silicon-carbide (SiC) single-walled nanotubes. For each nanotube, the effect of tube radius on the surface potentials and calculated average local ionization energies was investigated.

2605-2612 **An implementation of hydrophobic force in implicit solvent molecular dynamics simulation for packed proteins** Li L. Duan, Tong Zhu, Ye Mei, Qing G. Zhang, Bo Tang, John Z. H. Zhang[East China Normal University]

See Applications / Protein Dynamics.

2613-2623 **Structure of dipeptides having N-terminal selenocysteine residues: a DFT study in gas and aqueous phase** Shilpi Mandal, Gunajyoti Das [North Eastern Hill University]

See Methodology / QM and QM/MM.

2625-2633 **The substitution reaction of (CNC)Fe–2$N_2$with CO** Hongyan Liu, Shuangshuang Liu, Xiang Zhang [Shanxi Normal Uniovsersity]

The substitution mechanism of two N_2 ligands in (CNC)Fe–2N_2 replaced by CO was studied theoretically at the B3LYP/LACVP* level.

2635-264 5**Molecular dynamic simulations give insight into the mechanism of binding between 2-aminothiazole inhibitors and CDK5** Wei Wang, Xiaoning Cao, Xiaolei Zhu [**Nanjing University of Technology,]**, Yongliang Gu

See Applications / Ligand Binding.

2647-2656 **Influence of C-terminal tail deletion on structure and stability of hyperthermophile Sulfolobus tokodaii RNase HI** Lin Chen, Ji-Long Zhang, Qing-Chuan Zheng, Wen-Ting Chu, Qiao Xue, Hong-Xing Zhang [Jilin University], Chia-Chung Sun

See Applications / Protein Structure Prediction.

Journal of Molecular Graphics and Modelling, 44, June, 2013.

1-8 **In silico bioremediation of polycyclic aromatic hydrocarbon: A frontier in environmental chemistry** Vito Librandoa [Università di Catania] , Matteo Pappalardoa,

In this review, we present an overview of recent work investigating enzyme degradation of polycyclic aromatic hydrocarbons.

9–16 **MD and QM/MM study on catalytic mechanism of a FAD-dependent enzyme ORF36: For nitro sugar biosynthesi**s Yanwei Li, Lei Ding, Qingzhu Zhang [Shandong University] , Wenxing Wang

See Methodology / QM and QM/MM.

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1. APPLICATIONS

1.1. *Small Molecules*

Medicinal Chemistry and Drug Design

Photoexpulsion of Surface-Grafted Ruthenium Complexes and Subsequent Release of Cytotoxic Cargos to Cancer Cells from Mesoporous Silica Nanoparticles

Marco Frasconi, Zhichang Liu, Juying Lei, Yilei Wu, Elena Strekalova, Dmitry Malin, Michael W. Ambrogio, Xinqi Chen, Youssry Y. Botros, Vincent L. Cryns, Jean-Pierre Sauvage, and J. Fraser Stoddart [Northwestern University]

J. Am. Chem. Soc., 2013, **135**, 11603–11613

Ruthenium(II) polypyridyl complexes have emerged both as promising probes of DNA structure and as anticancer agents because of their unique photophysical and cytotoxic properties. A key consideration in the administration of those therapeutic agents is the optimization of their chemical reactivities to allow facile attack on the target sites, yet avoid unwanted side effects. Here, we present a drug delivery platform technology, obtained by grafting the surface of mesoporous silica nanoparticles (MSNPs) with ruthenium(II) dipyridophenazine (dppz) complexes.

Computational design of a CNT carrier for a high affinity bispecific anti-HER2 antibody based on trastuzumab and pertuzumab Fabs

Karim Salazar-Salinas, Carlos Kubli-Garfias, Jorge M. Seminario [Texas A&M University]

J. Mol.Mod., **19,** 2797-2810, 2013.

A! & S!

We study the main interactions between the antibody and the antigen by a computational scanning mutagenesis approach of trastuzumab and pertuzumab fragment antigen binding (Fab) structures in order to enhance their binding affinity. Then, each Fab fragments is joined by a polypeptide linker which should be stable enough to avoid the "open form" of antibody. On the other hand, we also conjugate the engineered antibody to functionalized CNTs (f-CNTs), which encapsulate the inhibitors of the HER2/PI3K/Akt/mTOR signaling pathway. We take advantage of the fact that f-CNT converts the RF radiation absorption into heat release.

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Medicinal Chemistry and Drug Design (Cont'd)

Revisiting a Receptor-Based Pharmacophore Hypothesis for Human A2A Adenosine Receptor Antagonists

Magdalena Bacilieri, Antonella Ciancetta, Silvia Paoletta, Stephanie Federico, Sandro Cosconati, Barbara Cacciari, Sabrina Taliani, Federico Da Settimo, Ettore Novellino, Karl Norbert Klotz, Giampiero Spalluto, and Stefano Moro [Università di Padova,]

J.Chem. Infor. and Mod. **53**, 1620–1637, 2013.

The application of both structure- and ligand-based design approaches represents to date one of the most useful strategies in the discovery of new drug candidates. In the present paper, we investigated how the application of docking-driven conformational analysis can improve the predictive ability of 3D-QSAR statistical models. With the use of the crystallographic structure in complex with the high affinity antagonist ZM 241385 (4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol),

Time-Resolved Spectroscopic Characterization of a Novel Photodecarboxylation Reaction Mediated by Homolysis of a Carbon α-Bond in Flurbiprofen

Tao Su, Jiani Ma, Naikei Wong, and David Lee Phillips [The University of Hong Kong,]

J. Phys. Chem. B., **117**, 8347–8359, 2013**.**

In this study, the photodecarboxylation reaction of Fp, which has been assumed to underpin its photoinduced side effects, was explored by femtosecond transient absorption (fs-TA), nanosecond transient absorption (ns-TA), and nanosecond time-resolved resonance Raman (ns-TR3) spectroscopic techniques in pure acetonitrile (MeCN) solvent. Density functional theory (DFT) calculations were also performed to facilitate the assignments of transient species.

Quantitative Structure-Activity Relations

Structural requirements of 3-carboxyl-4(1H)-quinolones as potential antimalarials from 2D and 3D QSAR analysis

Jiazhong Li [Lanzhou University], Shuyan Li, Chongliang Bai, Huanxiang Liu, Paola Gramatica

J. Mol.Graph. and Mod., **44,** 266–277 2013.

Many commonly available antimalarial drugs and therapies are becoming ineffective because of the emergence of multidrug resistant *Plasmodium falciparum*, which drives the need for the development of new antimalarial drugs. In this study, to analyze the structure–activity relationships (SAR) of these quinolones and investigate the structural requirements for antimalarial activity, the 2D multiple linear regressions (MLR) method and 3D CoMFA and CoMSIA methods are employed to evolve different QSAR models. All these models give satisfactory results with highly accurate fitting and strong external predictive abilities for chemicals not used in model development.

Molecular Modeling of p38α Mitogen-Activated Protein Kinase Inhibitors through 3D-QSAR and Molecular Dynamics Simulations

Hsin-Wen Chang , Fu-Sheng Chung and Chia-Ning Yang[National University of Kaohsiung]

J.Chem. Infor. and Mod. **53**, 1775–1786, 2013.

The p38 mitogen-activated protein kinase (MAPK) signaling pathway plays an essential role in inflammation and other physiological processes. Because specific inhibitors of p38α and p38β MAPK block the production of the major inflammatory cytokines and other proteins, p38α and p38β MAPK represent promising targets for the treatment of inflammation. In this work, a series of p38α inhibitors based on the structural scaffold of 4-benzoyl-5-aminopyrazole were analyzed using a combination of molecular modeling techniques.

Host-Guest Systems

Large Scale Affinity Calculations of Cyclodextrin Host–Guest Complexes: Understanding the Role of Reorganization in the Molecular Recognition Process

Lauren Wickstrom, Peng He, Emilio Gallicchio, and Ronald M. Levy [Rutgers University]

J. Chem. Theor. and Comp, **9**, 3136–3150, 2013.

Host–guest inclusion complexes are useful models for understanding the structural and energetic aspects of molecular recognition. Due to their small size relative to much larger protein–ligand complexes, converged results can be obtained rapidly for these systems thus offering the opportunity to more reliably study fundamental aspects of the thermodynamics of binding. In this work, we have performed a large scale binding affinity survey of 57 β-cyclodextrin (CD) host–guest systems using the binding energy distribution analysis method (BEDAM) with implicit solvation (OPLS-AA/AGBNP2).

Host–Guest Chemistry from Solution to the Gas Phase: An Essential Role of Direct Interaction with Water for High-Affinity Binding of Cucurbit[n]urils

Shin Jung C. Lee, Jong Wha Lee, Hong Hee Lee, Jongcheol Seo, Dong Hun Noh, Young Ho Ko, Kimoon Kim, and Hugh I. Kim [University of Science and Technology (POSTECH)]

J. Phys. Chem. B., **117**, 8855–8864, 2013**.**

An investigation of the host–guest chemistry of cucurbit[n]uril (CB[n], n = 6 and 7) with α,ω-alkyldiammonium guests (H2N(CH2)xNH2, x = 4, 6, 8, 10, and 12) both in solution and in the gas phase elucidates their intrinsic host–guest properties and the contribution of solvent water. Isothermal titration calorimetry and nuclear magnetic resonance measurements indicate that all alkyldiammonium cations have inclusion interactions with CB[n] except for the CB[7]–tetramethylenediamine complex in aqueous solution.

Molecular Dynamics Study of β-Cyclodextrin–Phenylalanine (1:1) Inclusion Complex in Aqueous Medium

Madhurima Jana and Sanjoy Bandyopadhyay [Indian Institute of Technology]

J. Phys. Chem. B., **117**, 9280–9287, 2013**.**

Atomistic molecular dynamics (MD) simulations of host–guest inclusion complexes of β-cyclodextrin (BCD) and zwitterionic phenylalanine (zPHE) following two possible orientations of zPHE in aqueous solutions have been carried out. The guest induced structural changes of BCD and the microscopic properties of surrounding water have been explored. The results obtained for the complex molecules were compared with those obtained for free BCD and free zPHE molecules. It is found that irrespective of the orientation, the complexation of BCD and zPHE (1:1) is associated with loss of configurational entropy.

Zeolites

SSZ-52, a Zeolite with an 18-Layer Aluminosilicate Framework Structure Related to That of the DeNOx Catalyst Cu-SSZ-13

Dan Xie, Lynne B. McCusker, Christian Baerlocher, Stacey I. Zones [Chevron Energy Technology Company], Wei Wan, and Xiaodong Zou

J. Am. Chem. Soc., 2013, **135**, 10519–10524

A new zeolite (SSZ-52, |(C14H28N)6Na6(H2O)18|[Al12Si96O216]), related to the DeNOx catalyst Cu-SSZ-13 (CHA framework type), has been synthesized using an unusual polycyclic quaternary ammonium cation as the structure-directing agent. By combining X-ray powder diffraction (XPD), high-resolution transmission electron microscopy (HRTEM) and molecular modeling techniques, its porous aluminosilicate framework structure ($R\bar{3}m$, a = 13.6373(1) Å,c = 44.7311(4) Å), which can be viewed as an 18-layer stacking sequence of hexagonally arranged (Si,Al)6O6 rings (6-rings), has been elucidated.

Carbon Nanoparticles

Anisotropic Dielectric Relaxation of the Water Confined in Nanotubes for Terahertz Spectroscopy Studied by Molecular Dynamics Simulations

Wenpeng Qi, Jige Chen, Junwei Yang, Xiaoling Lei, Bo Song [Chinese Academy of Sciences,], and Haiping Fang

J. Phys. Chem. B., **117**, 7967–7971, 2013**.**

The dynamics and structure of the hydrogen-bond network in confined water are of importance in understanding biological and chemical processes. Recently, terahertz (THz) time domain spectroscopy was widely applied for studying the kinetics of molecules and the hydrogen-bond network in water. However, the characteristics of the THz spectroscopy varying with respect to the confinement and the mechanism underlying the variation are still unclear. Here, on the basis of molecular dynamics simulations, the relationship between the anisotropic dielectric relaxation and the structure of the water confined in a carbon nanotube (CNT) was investigated.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

PHAISTOS: A framework for Markov chain Monte Carlo simulation and inference of protein structure

Wouter Boomsma [University of Copenhagen], Jes Frellsen, Tim Harder, Sandro Bottaro, Kristoffer E. Johansson, Pengfei Tian, Kasper Stovgaard, Christian Andreetta, Simon Olsson, Jan B. Valentin, Lubomir D. Antonov, Anders S. Christensen, Mikael Borg, Jan H. Jensen, Kresten Lindorff-Larsen, Jesper Ferkinghoff-Borg,homas Hamelryc

J. Comp. Chem., **34**, 1697–1705, 2013.

We present a new software framework for Markov chain Monte Carlo sampling for simulation, prediction, and inference of protein structure. The software package contains implementations of recent advances in Monte Carlo methodology, such as efficient local updates and sampling from probabilistic models of local protein structure. These models form a probabilistic alternative to the widely used fragment and rotamer libraries. Combined with an easily extendible software architecture, this makes PHAISTOS well suited for Bayesian inference of protein structure from sequence and/or experimental data.

Bioinformatics and Cheminformatics (Cont'd)

DOT2: Macromolecular docking with improved biophysical models

Victoria A. Roberts[University of California] , Elaine E. Thompson, Michael E. Pique, Martin S. Perez, L. F. Ten Eyck

J. Comp. Chem., **34**, 1743–1758, 2013.

Computational docking is a useful tool for predicting macromolecular complexes, which are often difficult to determine experimentally. Here, we present the DOT2 software suite, an updated version of the DOT intermolecular docking program. DOT2 provides straightforward, automated construction of improved biophysical models based on molecular coordinates, offering checkpoints that guide the user to include critical features.

The emerging role of cloud computing in molecular modeling

Jean-Paul Ebejer, Simone Fulle, Garrett M. Morris, Paul W. Finn[Oxford Centre for Innovation,]

J. Mol.Graph. and Mod., **44,**177–187, 2013.

The distinguishing features of cloud computing and their relationship to other distributed computing paradigms are described, as are the strengths and weaknesses of the approach. We review the use made to date of cloud computing for molecular modelling projects and the availability of front ends for molecular modelling applications. Although the use of cloud computing technologies for molecular modelling is still in its infancy, we demonstrate its potential by presenting several case studies.

AutoGrow 3.0: An improved algorithm for chemically tractable, semi-automated protein inhibitor design

Jacob D. Durrant [University of California San Diego], Steffen Lindert, J. Andrew McCammon

J. Mol.Graph. and Mod., **44,** 104–112, 2013.

We here present an improved version of AutoGrow (version 3.0), an evolutionary algorithm that works in conjunction with existing open-source software to automatically optimize candidate ligands for predicted binding affinity and other druglike properties. Though no substitute for the medicinal chemist, AutoGrow 3.0, unlike its predecessors, attempts to introduce some chemical intuition into the automated optimization process. AutoGrow 3.0 uses the rules of click chemistry to guide optimization, greatly enhancing synthesizability.

VAMMPIRE: A Matched Molecular Pairs Database for Structure-Based Drug Design and Optimization

Julia Weber, Janosch Achenbach, Daniel Moser, and Ewgenij Proschak [Goethe-University]

J.Med.Chem., **56,** 5203–5207, 2013.

S!

Structure-based optimization to improve the affinity of a lead compound is an established approach in drug discovery. Knowledge-based databases holding molecular replacements can be supportive in the optimization process. We introduce a strategy to relate the substitution effect within matched molecular pairs (MMPs) to the atom environment within the cocrystallized protein–ligand complex.

Bioinformatics and Cheminformatics (Cont'd)

DOLINA – Docking Based on a Local Induced-Fit Algorithm: Application toward Small-Molecule Binding to Nuclear Receptors

Martin Smieško[University of Basel,]

J.Chem. Infor. and Mod. **53**, 1415–1423, 2013.

Docking algorithms allowing for ligand and – to various extent – also protein flexibility are nowadays replacing techniques based on rigid protocols. The algorithm implemented in the Dolina software relies on pharmacophore matching for generating potential ligand poses and treats associated local induced-fit changes by combinatorial rearrangement of side-chains lining the binding site. In Dolina, ligand flexibility is not treated internally, instead a pool of low-energy conformers identified in a conformational search is screened for extended binding-pose candidates

Evaluation and Optimization of Virtual Screening Workflows with DEKOIS 2.0 – A Public Library of Challenging Docking Benchmark Sets

Matthias R. Bauer, Tamer M. Ibrahim, Simon M. Vogel, and Frank M. Boeckler [Eberhard Karls University Tuebingen,]

J.Chem. Infor. and Mod. **53**, 1447–1462, 2013.

S!

The application of molecular benchmarking sets helps to assess the actual performance of virtual screening (VS) workflows. To improve the efficiency of structure-based VS approaches, the selection and optimization of various parameters can be guided by benchmarking. With the DEKOIS 2.0 library, we aim to further extend and complement the collection of publicly available decoy sets. Based on BindingDB bioactivity data, we provide 81 new and structurally diverse benchmark sets for a wide variety of different target classes.

MODYLAS: A Highly Parallelized General-Purpose Molecular Dynamics Simulation Program for Large-Scale Systems with Long-Range Forces Calculated by Fast Multipole Method (FMM) and Highly Scalable Fine-Grained New Parallel Processing Algorithms

Yoshimichi Andoh, Noriyuki Yoshii, Kazushi Fujimoto, Keisuke Mizutani, Hidekazu Kojima, Atsushi Yamada, Susumu Okazaki [Kanazawa University], Kazutomo Kawaguchi, Hidemi Nagao, Kensuke Iwahashi, Fumiyasu Mizutani, Kazuo Minami, Shin-ichi Ichikawa, Hidemi Komatsu, Shigeru Ishizuki, Yasuhiro Takeda, and Masao Fukushima

J. Chem. Theor. and Comp, **9**, 3201–3209, 2013.

A!

Our new molecular dynamics (MD) simulation program, MODYLAS, is a general-purpose program appropriate for very large physical, chemical, and biological systems. It is equipped with most standard MD techniques. Long-range forces are evaluated rigorously by the fast multipole method (FMM) without using the fast Fourier transform (FFT). Several new methods have also been developed for extremely fine-grained parallelism of the MD calculation. The virtually buffering-free methods for communications and arithmetic operations, the minimal communication latency algorithm, and the parallel bucket-relay communication algorithm for the upper-level multipole moments in the FMM realize excellent scalability.

Bioinformatics and Cheminformatics (Cont'd)

PRIMO: **A Transferable Coarse-Grained Force Field for Proteins**

Parimal Kar, Srinivasa Murthy Gopal, Yi-Ming Cheng, Alexander Predeus, and Michael Feig [Michigan State University,]

J. Chem. Theor. and Comp, **9**, 3769–3788, 2013.

A!

We describe here the PRIMO (protein intermediate model) force field, a physics-based fully transferable additive coarse-grained potential energy function that is compatible with an all-atom force field for multiscale simulations. The energy function consists of standard molecular dynamics energy terms plus a hydrogen-bonding potential term and is mainly parametrized based on the CHARMM22/CMAP force field in a bottom-up fashion. The solvent is treated implicitly via the generalized Born model. The bonded interactions are either harmonic or distance-based spline interpolated potentials. These potentials are defined on the basis of all-atom molecular dynamics (MD) simulations of dipeptides with the CHARMM22/CMAP force field.

Boosting Virtual Screening Enrichments with Data Fusion: Coalescing Hits from Two-Dimensional Fingerprints, Shape, and Docking

G. Madhavi Sastry, V. S. Sandeep Inakollu [Schrödinger, Sanali Infopark], and Woody Sherman

J.Chem. Infor. and Mod. **53**, 1531–1542, 2013.

S!

Virtual screening is an effective way to find hits in drug discovery, with approaches ranging from fast information-based similarity methods to more computationally intensive physics-based docking methods. However, the best approach to use for a given project is not clear in advance of the screen. In this work, we show that combining results from multiple methods using a standard score (Z-score) can significantly improve virtual screening enrichments over any of the single screening methods.

Protein Secondary Structure

Porter, PaleAle 4.0: high-accuracy prediction of protein secondary structure and relative solvent accessibility

Claudio Mirabello and Gianluca Pollastri [University College Dublin]

Bioinformatics. **29**, 2056-2058, 2013.

Protein secondary structure and solvent accessibility predictions are a fundamental intermediate step towards protein structure and function prediction. We present new systems for the *ab initio*prediction of protein secondary structure and solvent accessibility, Porter 4.0 and PaleAle 4.0. Porter 4.0 predicts secondary structure correctly for 82.2% of residues. PaleAle 4.0's accuracy is 80.0% for prediction in **two**classes with a 25% accessibility threshold. We show that the increasing training set sizes that come with the continuing growth of the Protein Data Bank keep yielding prediction quality improvements and examine the impact of protein resolution on prediction performances.

Protein Secondary Structure (Cont'd)

Multiscale simulations of protein folding: application to formation of secondary structures

Ji Xu, Ying Ren & Jinghai Li [Chinese Academy of Sciences]

J. Biomol. Stru. and Dyn., ***31***, 779-787, *2013.*

A multiscale simulation method of protein folding is proposed, using atomic representation of protein and solvent, combing genetic algorithms to determine the key protein structures from a global view, with molecular dynamic simulations to reveal the local folding pathways, thus providing an integrated landscape of protein folding. The method is found to be superior to previously investigated global search algorithms or dynamic simulations alone.

Protein Structure prediction

PconsD: ultra rapid, accurate model quality assessment for protein structure prediction

Marcin J. Skwark and Arne Elofsson[Stockholm University]

Bioinformatics. **29**, 1817-1818, 2013.

Clustering methods are often needed for accurately assessing the quality of modeled protein structures. Recent blind evaluation of quality assessment methods in CASP10 showed that there is little difference between many different methods as far as ranking models and selecting best model are concerned. When comparing many models, the computational cost of the model comparison can become significant. Here, we present PconsD, a fast, stream-computing method for distance-driven model quality assessment that runs on consumer hardware. PconsD is at least one order of magnitude faster than other methods of comparable accuracy.

Multiobjective evolutionary algorithm with many tables for purely ab initio protein structure prediction

Christiane Regina Soares Brasil[University of São Paulo],Alexandre Claudio Botazzo Delbem,Fernando Luís Barroso da Silva

J. Comp. Chem., **34**, 1719–1734, 2013.

This article focuses on the development of an approach for ab initio protein structure prediction (PSP) without using any earlier knowledge from similar protein structures, as fragment-based statistics or inference of secondary structures. Such an approach is called purely ab initio prediction. The article shows that well-designed multiobjective evolutionary algorithms can predict relevant protein structures in a purely ab initio way. One challenge for purely ab initio PSP is the prediction of structures with β-sheets. To work with such proteins, this research has also developed procedures to efficiently estimate hydrogen bond and solvation contribution energies.

Protein Structure Prediction (Cont'd)

High–quality protein backbone reconstruction from alpha carbons using gaussian mixture models

Benjamin L. Moore, Lawrence A. Kelley,James Barber, James W. Murray, James T. MacDonald[South Kensington Campus, London,]

J. Comp. Chem., **34**, 1881–1889, 2013.

Coarse-grained protein structure models offer increased efficiency in structural modeling, but these must be coupled with fast and accurate methods to revert to a full-atom structure. Here, we present a novel algorithm to reconstruct mainchain models from C traces. This has been parameterized by fitting Gaussian mixture models (GMMs) to short backbone fragments centered on idealized peptide bonds. The method we have developed is statistically significantly more accurate than several competing methods, both in terms of RMSD values and dihedral angle differences.

A homology/*ab initio* hybrid algorithm for sampling near-native protein conformations

Priyanka Dhingra, Bhyravabhotla Jayaram[Indian Institute of Technology, Hauz Khas, New Delhi]

J. Comp. Chem., **34**, 1925–1936, 2013.

One of the major challenges for protein tertiary structure prediction strategies is the quality of conformational sampling algorithms, which can effectively and readily search the protein fold space to generate near-native conformations. In an effort to advance the field by making the best use of available homology as well as fold recognition approaches along with *ab initio* folding methods, we have developed*Bhageerath*-H Strgen, a homology/*ab initio* hybrid algorithm for protein conformational sampling.

A simple probabilistic model of multibody interactions in proteins

Kristoffer Enøe Johansson, Thomas Hamelryck[University of Copenhagen]

Proteins: Stru. Fun. & Bioinf., **81**, 1340–1350, 2013.

Protein structure prediction methods typically use statistical potentials, which rely on statistics derived from a database of know protein structures. In the vast majority of cases, these potentials involve pairwise distances or contacts between amino acids or atoms. Although some potentials beyond pairwise interactions have been described, the formulation of a general multibody potential is seen as intractable due to the perceived limited amount of data. In this article, we show that it is possible to formulate a probabilistic model of higher order interactions in proteins, without arbitrarily limiting the number of contacts.

Bifurcated Hydrogen Bonding and Asymmetric Fluctuations in a Carbohydrate Crystal Studied via X-ray Crystallography and Computational Analysis

Xibing He, Elizabeth Hatcher, Lars Eriksson, Göran Widmalm [University of Maryland,], and Alexander D. MacKerell, Jr.

J. Phys. Chem. B., **117**, 7546–7553, 2013**.**

The structure of the O-methyl glycoside of the naturally occurring 6-O-[(R)-1-carboxyethyl]-α-D-galactopyranose, C10H18O8, has been determined by X-ray crystallography at 100 K, supplementing the previously determined structure obtained at 293 K (Acta Crystallogr.1996, C52, 2285–2287). MD simulations of this glycoside were performed in the crystal environment with different numbers of units cells included in the primary simulation system at both 100 and 293 K. The calculated unit cell parameters and the intramolecular geometries (bonds, angles, and dihedrals) agree well with experimental results. Atomic fluctuations, including B-factors and anisotropies, are in good agreement with respect to the relative values on an atom-by-atom basis.

Comparative or Homology Modeling

Homology modeling study toward identifying structural properties in the HA2 B-loop that would influence the HA1 receptor-binding site

Marni E. Cueno, Kenichi Imai, Kazufumi Shimizu, Kuniyasu Ochiai [Nihon University School of Dentistry]

J. Mol.Graph. and Mod., **44,** 161–167, 2013.

Influenza hemagglutinin (HA) consists of a fibrous globular stem (HA2) inserted into the viral membrane supporting a globular head (HA1). HA1 receptor-binding has been hypothesized to be structurally correlated to the HA2 B-loop, however, this was never fully understood. Here, we elucidated the structural relationship between the HA2 B-loop and the HA1 receptor-binding site (RBS). Throughout this study, we analyzed 2486 H1N1 HA homology models obtained from human, swine and avian strains during 1976–2012.

Gene identification and comparative molecular modeling of a *Trypanosoma rangeli* major surface protease

Paulo H. M. Calixto, Mainá Bitar, Keila A. M. Ferreira, Odonírio Abrahão Jr., Eliane Lages-Silva,Glória R. Franco, Luis E. Ramírez, André L. Pedrosa [Universidade Federal do Triângulo Mineiro,

J. Mol.Mod., **19,** 3053-3064, 2013.

The aims of this work were to generate the complete sequence of a *T. rangeli* MSP (TrMSP) gene and to determine the 3D-structure of the predicted protein by homology modeling. The plasmid bearing a complete copy of a TrMSP gene was completely sequenced and the predicted protein was modeled using Modeller software. Results indicate that TrMSP open reading frame (ORF) codes for a predicted 588 amino acid protein and shows all elements required for its posttranslational processing.

Insight into the 3D structure of ADP-glucose pyrophosphorylase from rice (*Oryza sativa* L.)

Chhavi Dawar, Sunita Jain, Sudhir Kumar [CCS Haryana Agricultural University]

J. Mol.Mod., **19,** 3351-3367, 2013.

ADP-glucose pyrophosphorylase (E.C. 2.7.7.27; AGPase) is a key regulatory enzyme that catalyzes the rate-limiting step of starch biosynthesis in higher plants. AGPase consists of pair of small (SS) and large (LS) subunits thereby constituting a heterotetrameric structure. No crystal structure of the native heterotetrameric enzyme is available for any species, thus limiting the complete understanding of structure–function relationships of this enzyme. In this study, an attempt was made to deduce the heterotetrameric assembly of AGPase in rice.

Structural Basis for the Mutation-Induced Dysfunction of Human CYP2J2: A Computational Study

Shan Cong, Xiao-Tu Ma, Yi-Xue Li, and Jing-Fang Wang [Shanghai Jiao Tong University]

J.Chem. Infor. and Mod. **53**, 1350–1357, 2013.

Arachidonic acid is an essential fatty acid in cells, acting as a key inflammatory intermediate in inflammatory reactions. In cardiac tissues, CYP2J2 can adopt arachidonic acid as a major substrate to produce epoxyeicosatrienoic acids (EETs), which can protect endothelial cells from ischemic or hypoxic injuries and have been implicated in the pathogenesis of coronary artery disease and hypertension. In the current study, three-dimensional structural models of the wild-type CYP2J2 and two mutants (T143A and N404Y) were constructed by a coordinate reconstruction approach and ab initio modeling using CYP2R1 as a template.

Comparative or Homology Modeling (Cont'd)

Murine mPGES-1 3D Structure Elucidation and Inhibitors Binding Mode Predictions by Homology Modeling and Site-Directed Mutagenesis

Gaia Corso, Isabella Coletta, and Rosella Ombrato [Angelini Research Center,]

J.Chem. Infor. and Mod. **53**, 1804–1817, 2013.

S!

Microsomal prostaglandin E synthase-1 (mPGES-1) constitutes an inducible glutathione-dependent integral membrane protein that catalyzes the oxido-reduction of cyclooxygenase derived PGH2 into PGE2. mPGES-1 is an essential enzyme involved in a variety of human diseases or pathological conditions, such as rheumatoid arthritis, fever, and pain; it is therefore regarded as a primary target for development of next-generation anti-inflammatory drugs. The current study focuses on the elucidation of the molecular determinants of murine mPGES-1 ligand binding modes combining protein homology modeling and site-directed mutagenesis approaches.

Protein Confirmational Analysis

Application of replica exchange umbrella sampling to protein structure refinement of nontemplate models

Mark A. Olson[USAMRIID, Fredrick], Michael S. Lee

J. Comp. Chem., **34**, 1785–1793, 2013.

We provide an assessment of a computational strategy for protein structure refinement that combines self-guided Langevin dynamics with umbrella-potential biasing replica exchange using the radius of gyration as a coordinate (Rg-ReX). Eight structurally nonredundant proteins and their decoys were examined by sampling conformational space at room temperature using the CHARMM22/GBMV2 force field to generate the ensemble of structures. Two atomic statistical potentials (RWplus and DFIRE) were analyzed for structure identification and compared to the simulation force-field potential.

Retrospective molecular docking study of WY-25105 ligand to β-secretase and bias of the three-dimensional structure flexibility

Leo Ghemtio, Nicolas Muzet[R&D, Sanofi Aventis,]

J. Mol.Mod., **19,** 2971-2979, 2013.

β-Secretase (BACE) is a very promising target in the search for a treatment for Alzheimer's disease using a protein–ligand inhibition approach. Given the many published X-ray structures of BACE protein, structure-based drug design has been used extensively to support new inhibitor discovery programs. In the present retrospective study, a set of available X-ray enzyme structures was selected and molecular dynamics simulations were conducted to generate more diverse representative BACE protein conformations.

Estimation of Ligand Efficacies of Metabotropic Glutamate Receptors from Conformational Forces Obtained from Molecular Dynamics Simulations

Sirish Kaushik Lakkaraju , Fengtian Xue , Alan I. Faden , and Alexander D. MacKerell [University of Maryland,]

J.Chem. Infor. and Mod. **53**, 1337–1349, 2013.

Group 1 metabotropic glutamate receptors (mGluR) are G-protein coupled receptors with a large bilobate extracellular ligand binding region (LBR) that resembles a Venus fly trap. Closing of this LBR in the presence of a ligand is associated with the activation of the receptor. From conformational sampling of the LBR–ligand complexes using all-atom molecular dynamics (MD) simulations, we characterized the conformational minima related to the hinge like motion associated with the LBR closing/opening in the presence of known agonists and antagonists.

Protein Confirmational Analysis (Cont'd)

Rapid Conformational Fluctuations of Disordered HIV-1 Fusion Peptide in Solution

Tom Venken, Arnout Voet, Marc De Maeyer, Gianni De Fabritiis, and S. Kashif Sadiq [Universitat Pompeu Fabra,]

J. Chem. Theor. and Comp, **9**, 2870–2874, 2013.

The conformationally flexible fusion peptide (FP) of HIV-1 is indispensible for viral infection of host cells, due to its ability to insert into and tightly couple with phospholipid membranes. There are conflicting reports on the membrane-associated structure of FP, and solution structure information is limited, yet such a structure is the target for a novel class of antiretroviral inhibitors. An ensemble of explicit solvent MD simulations, initiated from a disordered HIV-1 FP, revealed that while the vast majority of conformations predominantly lack secondary structure, both spontaneous formation and rapid interconversion of local secondary structure elements occur, highlighting the structural plasticity of the peptide.

Learning Kinetic Distance Metrics for Markov State Models of Protein Conformational Dynamics

Robert T. McGibbon and Vijay S. Pande [Stanford University,]

J. Chem. Theor. and Comp, **9**, 2900–2906, 2013.

Statistical modeling of long timescale dynamics with Markov state models (MSMs) has been shown to be an effective strategy for building quantitative and qualitative insight into protein folding processes. Existing methodologies, however, rely on geometric clustering using distance metrics such as root mean square deviation (RMSD), assuming that geometric similarity provides an adequate basis for the kinetic partitioning of phase space. Here, inspired by advances in the machine learning community, we introduce a new approach for learning a distance metric explicitly constructed to model kinetic similarity.

Copper-chaperones with dicoordinated Cu(I)—Unique protection mechanism

Tamar Ansbacher, Mukesh Chourasia and Avital Shurki [The Hebrew University of Jerusalem,]

Proteins: Stru. Fun. & Bioinf., **81**, 1411–1419, 2013.

Cu(I) dicoordination with thiolate ligands is not common. Yet, different from its homologue proteins, human copper chaperone is known to bind Cu(I) using this low coordination number while binding Cu(I) only via the two conserved Cysteine residues, Cys12 and Cys15. Based on structural analysis, this work determines that the protein possesses two distinct conformations referred to as "in" and "out" due to the relative positioning of Cys12 (one of Cu(I) binding residues). The "out" conformation, with Cys12 pointing out, imposes a buried Cu(I) position, whereas the "in" conformation with Cys12 pointing inwards results in a more exposed Cu(I) thus, available for transfer.

Thermostabilization of the β1-Adrenergic Receptor Correlates with Increased Entropy of the Inactive State

Michiel J. M. Niesen, Supriyo Bhattacharya, Reinhard Grisshammer, Christopher G. Tate, and Nagarajan Vaidehi [Beckman Research Institute of the City of Hope,]

J. Phys. Chem. B., **117**, 7283–7291, 2013**.**

The dynamic nature of GPCRs is a major hurdle in their purification and crystallization. Thermostabilization can facilitate GPCR structure determination, as has been shown by the structure of the thermostabilized β1-adrenergic receptor (β1AR) mutant, m23-β1AR, which has been thermostabilized in the inactive state. However, it is unclear from the structure how the six thermostabilizing mutations in m23-β1AR affect receptor dynamics. We have used MD simulations in explicit solvent to compare the conformational ensembles for both wild type β1AR (wt-β1AR) and m23-β1AR.

Protein Confirmational Analysis (Cont'd)

Conformational Study of GSH and GSSG Using Constant-pH Molecular Dynamics Simulations

Diogo Vila-Viçosa , Vitor H. Teixeira , Hugo A. F. Santos , and Miguel Machuqueiro [Universidade de Lisboa]

J. Phys. Chem. B., **117**, 7507–7517, 2013**.**

Glutathione is a small peptide with a crucial role in living organisms. This molecule is found in Nature in both reduced (GSH) and oxidized (GSSG) forms and a high GSH/GSSG ratio is essential to the cell. Glutathione is also present in several enzymatic reactions and can be found in many protein structures. Here, we present a detailed conformational study of GSH and GSSG in a range of pH values, together with a full pH titration of these molecules. We performed constant-pH MD simulations of GSH and GSSG at 24 pH values in a total of 14.4 μs (300 ns per pH value).

Computational and Experimental Investigations into the Conformations of Cyclic Tetra-α/β-peptides

Mark T. Oakley, Emmanuel Oheix, Anna F. A. Peacock, and Roy L. Johnston [University of Birmingham,]

J. Phys. Chem. B., **117**, 8122–8134, 2013**.**

We present a combined computational and experimental study of the energy landscapes of cyclic tetra-α/β-peptides. We have performed discrete path sampling calculations on a series of cyclic tetra-α/β-peptides to obtain the relative free energies and barriers to interconversion of their conformers. The most stable conformers of cyclo-[(β-Ala-Gly)2] contain all-trans peptide groups. The relative energies of the cis isomers and the cis–trans barriers are lower than in acyclic peptides but not as low as in the highly strained cyclic α-peptides.

pH-Dependent Conformational Ensemble and Polymorphism of Amyloid-β Core Fragment

Weixin Xu, Ce Zhang, Ludmilla Morozova-Roche, John Z. H. Zhang, and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B., **117**, 8392–8399, 2013**.**

Characterization of amyloid oligomeric species is important due to its possible responsibility for the toxicity of amyloid proteins, whereas it is difficult to detect by current spectroscopic techniques. The pH-dependent tetramerization and fibrillation of the central hydrophobic segment of Alzheimer amyloid β-peptide (Aβ12– 24) were respectively explored by all-atom replica exchange molecular dynamics simulations and by fluorescence and atomic force microscopy measurements.

Protein Structure Analysis

Proteomics Guided Discovery of Flavopeptins: Anti-proliferative Aldehydes Synthesized by a Reductase Domain-Containing Non-ribosomal Peptide Synthetase

Yunqiu Chen, Ryan A. McClure, Yupeng Zheng, Regan J. Thomson, and Neil L. Kelleher [Northwestern University]

J. Am. Chem. Soc., 2013, **135**, 10449–10456

Due to the importance of proteases in regulating cellular processes, the development of protease inhibitors has garnered great attention. Peptide-based aldehydes are a class of compounds that exhibit inhibitory activities against various proteases and proteasomes in the context of anti-proliferative treatments for cancer and other diseases. Herein we describe the discovery of a new group of lipopeptide aldehydes, the flavopeptins, and the corresponding biosynthetic pathway arising from an orphan gene cluster in Streptomyces sp. NRRL-F6652, a close relative ofStreptomyces flavogriseus ATCC 33331.

Protein Structure Analysis (Cont'd)

Dominant-negative effects in prion diseases: insights from molecular dynamics simulations on mouse prion protein chimeras

Xiaojing Cong, Salvatore Bongarzone, Gabriele Giachin, Giulia Rossetti, Paolo Carloni & Giuseppe Legname [Laboratory of Prion Biology, SISSA]

J. Biomol. Stru. and Dyn., ***31***, 829-840, *2013.*

Mutations in the prion protein (PrP) can cause spontaneous prion diseases in humans (Hu) and animals. In transgenic mice, mutations can determine the susceptibility to the infection of different prion strains. Some of these mutations also show a dominant-negative effect, thus halting the replication process by which wild type mouse (Mo) PrP is converted into Mo scrapie. Using all-atom molecular dynamics (MD) simulations, here we studied the structure of HuPrP, MoPrP, 10 Hu/MoPrP chimeras, and 1 Mo/sheepPrP chimera in explicit solvent.

Sequence and structural investigation of a novel psychrophilic α-amylase from*Glaciozyma antarctica* PI12 for cold-adaptation analysis

Aizi Nor Mazila Ramli, Mohd Akmal Azhar, Mohd Shahir Shamsir, Amir Rabu, Abdul Munir Abdul Murad, Nor Muhammad Mahadi, Rosli Md. Illias [Universiti Teknologi Malaysia]

J. Mol.Mod., **19,** 3369-3383, 2013.

A novel α-amylase was isolated successfully from *Glaciozyma antarctica* PI12 using DNA walking and reverse transcription-polymerase chain reaction (RT-PCR) methods. The structure of this psychrophilic α-amylase (AmyPI12) from *G. antarctica* PI12 has yet to be studied in detail. A 3D model of AmyPI12 was built using a homology modelling approach to search for a suitable template and to generate an optimum target–template alignment, followed by model building using MODELLER9.9.

A!

Protein Dynamics

Unraveling the Photoluminescence Response of Light-Switching Ruthenium(II) Complexes Bound to Amyloid-β

Nathan P. Cook, Mehmet Ozbil, Christina Katsampes, Rajeev Prabhakar, and Angel A. Martí [Rice University, Houston,]

J. Am. Chem. Soc., 2013, **135**, 10810–10816

Photoluminescent molecules are widely used for real-time monitoring of peptide aggregation. In this Article, we detail both experimental and computational modeling to elucidate the interaction between [Ru(bpy)2dppz]2+ and amyloid-β (Aβ1–40) aggregates. The transition from monomeric to fibrillar Aβ is of interest in the study of Alzheimer's disease. Concentration-dependent experiments allowed the determination of a dissociation constant of 2.1 μM, while Job plots provided a binding stoichiometry of 2.6 Aβ monomers per [Ru(bpy)2dppz]2+.

An insight to the dynamics of conserved water-mediated salt bridge interaction and interdomain recognition in hIMPDH isoforms

Hridoy R. Bairagya & Bishnu P. Mukhopadhyay[National Institute of Technology , Durgapur]

J. Biomol. Stru. and Dyn., ***31***, 788-808, *2013.*

Inosine monophosphate dehydrogenase (IMPDH) is involved in *de novo* biosynthesis pathway of guanosine nucleotide. Type II isoform of this enzyme is selectively upregulated in lymphocytes and chronic myelogenous leukemia (CML) cells, and is an excellent target for antileukemic agent. The MD simulation results (15 ns) of three unliganded 1B3O, 1JCN, and 1JR1 structures have clearly revealed that I_N, I_C (N- and C-terminal of catalytic domains) and C_1, C_2(cystathionine-beta-synthase-1 and 2) domains of IMPDH enzyme have been stabilized by six conserved water (center) mediated salt bridge interactions.

Protein Dynamics (Cont'd)

IMSPeptider: A computational peptide collision cross-section area calculator based on a novel molecular dynamics simulation protocol

Ranieri V. de Carvalho, Daniel Lopez-Ferrer, Katia S. Guimarães, Roberto D. Lins[Federal University of Pernambuco]

J. Comp. Chem., **34**, 1707–1718, 2013.

Introduction of ion mobility mass spectrometry (IMS/MS) into the proteomic workflow provides an orthogonal separation to the widely used LC-MS platforms. IMS also provides structural information that could facilitate peptide identification. However, the lack of tools capable of predictive power in a high-throughput fashion makes peptide global profiling quite challenging. To target this issue, a computational workflow was developed based on biophysical principles to predict the collision cross-section area (CCS) of peptides as measured from IMS/MS experiments.

Is the conformational flexibility of piperazine derivatives important to inhibit HIV-1 replication?

Cátia Teixeira [Univ Paris Diderot,], Nawal Serradji, Souad Amroune, Karen Storck, Christine Rogez-Kreuz, Pascal Clayette, Florent Barbault, François Maurel

J. Mol.Graph. and Mod., **44,** 91–103, 2013.

The conserved binding site of HIV-1 gp120 envelope protein, an essential component in the viral entry process, provides an attractive antiviral target. The structural similarities between two piperazine derivatives: PMS-601, showing a dual activity for anti-PAF and anti-HIV activity, and BMS-378806, known to inhibit HIV-1 gp120, motivated us to merge important structural features of the two compounds. We described an approach that combines molecular docking, molecular dynamics, MM-PBSA calculations and conformational analysis to rationally predict piperazine derivatives binding mode with HIV-1 gp120.

Structural and energetic properties of canonical and oxidized telomeric complexes studied by molecular dynamics simulations

Przemysław Czeleń [Nicolaus Copernicus University in Toruń,], Piotr Cysewski

J. Mol.Mod., **19,** 3339-3349, 2013.

The structural and energetic properties of native and oxidized telomeric complexes were defined by means of molecular dynamic (MD) simulations. As a starting point, the experimental conformation of B-DNA d(GpTpTpApGpGpGpTpTpApGpGpG) oligomer bound to human protein telomeric repeat binding factor 1 (TRF1) was used. The influence on the stability of the telomeric complex of the presence of 8-oxoguanine (8oxoG) in the central telomeric triad (CTT) was estimated based on trajectories collected during 130 ns MD runs.

Prediction of Cytochrome P450 Xenobiotic Metabolism: Tethered Docking and Reactivity Derived from Ligand Molecular Orbital Analysis

Jonathan D. Tyzack , Mark J. Williamson , Rubben Torella , and Robert C. Glen [Unilever Centre for Molecular Science Informatics, Cambridge]

J.Chem. Infor. and Mod. **53**, 1294–1305, 2013.

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Metabolism of xenobiotic and endogenous compounds is frequently complex, not completely elucidated, and therefore often ambiguous. The prediction of sites of metabolism (SoM) can be particularly helpful as a first step toward the identification of metabolites, a process especially relevant to drug discovery. This paper describes a reactivity approach for predicting SoM whereby reactivity is derived directly from the ground state ligand molecular orbital analysis, calculated using Density Functional Theory, using a novel implementation of the average local ionization energy.

Protein Dynamics (Cont'd)

Hydration Properties of Ligands and Drugs in Protein Binding Sites: Tightly-Bound, Bridging Water Molecules and Their Effects and Consequences on Molecular Design Strategies

Alfonso T. García-Sosa [University of Tartu,]

J.Chem. Infor. and Mod. **53**, 1388–1405, 2013.

Some water molecules in binding sites are important for intermolecular interactions and stability. The way binding site explicit water molecules are dealt with affects the diversity and nature of designed ligand chemical structures and properties. The strategies commonly employed frequently assume that a gain in binding affinity will be achieved by their targeting or neglect. However, in the present work, 2332 high-resolution X-ray crystal structures of hydrated and nonhydrated, drug and nondrug compounds in biomolecular complexes with reported Ki or Kd show that compounds that use tightly bound, bridging water molecules are as potent as those that do not.

Interactions and Stabilities of the UV RESISTANCE LOCUS8 (UVR8) Protein Dimer and Its Key Mutants

Min Wu, Åke Strid, and Leif A. Eriksson [University of Gothenburg,]

J.Chem. Infor. and Mod. **53**, 1736–1746, 2013.

The dimeric UVR8 protein is an ultraviolet-B radiation (280–315 nm) photoreceptor responsible for the first step in UV–B regulation of gene expression in plants. Its action comprises the actual absorption of the UV quanta by a tryptophan array at the protein–protein interface, followed by monomerization and subsequent aggregation with downstream signaling components. . In this work, molecular dynamics simulations in conjunction with umbrella sampling were used to calculate the binding free energy for the wild type UVR8 dimer and three of its mutants (R286A, R338A, and R286A/R338A), in order to verify whether the key mutants are able to disrupt the dimeric structure as indicated experimentally.

Effects of Temperature Control Algorithms on Transport Properties and Kinetics in Molecular Dynamics Simulations

Joseph E. Basconi and Michael R. Shirts [University of Virginia,]

J. Chem. Theor. and Comp, **9**, 2887–2899, 2013.

In this study, we investigate how six well-established thermostat algorithms applied with different coupling strengths and to different degrees of freedom affect the dynamics of various molecular systems. We consider dynamic processes occurring on different times scales by measuring translational and rotational self-diffusion as well as the shear viscosity of water, diffusion of a small molecule solvated in water, and diffusion and the dynamic structure factor of a polymer chain in water. All of these properties are significantly dampened by thermostat algorithms which randomize particle velocities, such as the Andersen thermostat and Langevin dynamics, when strong coupling is used.

Protein Dynamics (Cont'd)

Accurate Calculation of Mutational Effects on the Thermodynamics of Inhibitor Binding to p38α MAP Kinase: A Combined Computational and Experimental Study

Shun Zhu, Sue M. Travis, and Adrian H. Elcock [University of Iowa]

J. Chem. Theor. and Comp, **9**, 3151–3164, 2013.

A major current challenge for drug design efforts that are focused on protein kinases is the development of drug resistance caused by spontaneous mutations in the kinase catalytic domain. The ubiquity of this problem means that it would be advantageous to develop fast, effective computational methods that could be used to determine the effects of potential resistance-causing mutations before they arise in a clinical setting. With this long-term goal in mind, we have conducted a combined experimental and computational study of the thermodynamic effects of active-site mutations on a well-characterized and high-affinity interaction between a protein kinase and a small-molecule inhibitor.

Stability Mechanisms of Laccase Isoforms using a Modified FoldX Protocol Applicable to Widely Different Proteins

Niels J. Christensen and Kasper P. Kepp [Technical University of Denmark,]

J. Chem. Theor. and Comp, **9**, 3210–3223, 2013.

A recent computational protocol that accurately predicts and rationalizes protein multisite mutant stabilities has been extended to handle widely different isoforms of laccases. We apply the protocol to four isoenzymes of Trametes versicolor laccase (TvL) with variable lengths) and thermostability and with 67–77% sequence identity. The extended protocol uses (i) statistical averaging, (ii) a molecular-dynamics-validated "compromise" homology model to minimize bias that causes proteins close in sequence to a structural template to be too stable due to having the benefits of the better sampled template, (iii) correction for hysteresis that favors the input template to overdestabilize, and (iv) a preparative protocol to provide robust input sequences of equal length.

Molecule-Centered Method for Accelerating the Calculation of Hydrodynamic Interactions in Brownian Dynamics Simulations Containing Many Flexible Biomolecules

Adrian H. Elcock [University of Iowa]

J. Chem. Theor. and Comp, **9**, 3224–3239, 2013.

Inclusion of hydrodynamic interactions (HIs) is essential in simulations of biological macromolecules that treat the solvent implicitly if the macromolecules are to exhibit correct translational and rotational diffusion. The present work describes the development and testing of a simple approach aimed at allowing more rapid computation of HIs in coarse-grained Brownian dynamics simulations of systems that contain large numbers of flexible macromolecules.

Electrostatic-Consistent Coarse-Grained Potentials for Molecular Simulations of Proteins

Enrico Spiga, Davide Alemani, Matteo T. Degiacomi, Michele Cascella, and Matteo Dal Peraro [École Polytechnique Fédérale de Lausanne-EPFL]

J. Chem. Theor. and Comp, **9**, 3515–3526, 2013.

We present a new generation of coarse-grained (CG) potentials that account for a simplified electrostatic description of soluble proteins. The treatment of permanent electrostatic dipoles of the backbone and polar side-chains allows to simulate proteins, preserving an excellent structural and dynamic agreement with respective reference structures and all-atom MD simulations. Moreover, multiprotein complexes can be well described maintaining their molecular interfaces thanks to the ability of this scheme to better describe the actual electrostatics at a CG level of resolution.

Protein Dynamics (Cont'd)

Accurate prediction of hot spot residues through physicochemical characteristics of amino acid sequences

Peng Chen, Jinyan Li, Limsoon Wong, Hiroyuki Kuwahara, Jianhua Z. Huang and Xin Gao[King Abdullah University of Science and Technology (KAUST)

Proteins: Stru. Fun. & Bioinf., **81**, 1351–1362, 2013.

Hot spot residues of proteins are fundamental interface residues that help proteins perform their functions. Detecting hot spots by experimental methods is costly and time-consuming. Sequential and structural information has been widely used in the computational prediction of hot spots. However, structural information is not always available. In this article, we investigated the problem of identifying hot spots using only physicochemical characteristics extracted from amino acid sequences.

"Strange Kinetics" in the Temperature Dependence of Methionine Ligand Rebinding Dynamics in Cytochrome c

Ping Zhang, Steven Wooseok Ahn, and John E. Straub [Boston University]

J. Phys. Chem. B., **117**, 7190–7202, 2013**.**

The temperature dependence of methionine ligand dissociation and rebinding dynamics in cytochrome c in aqueous solution has been studied using classical molecular dynamics simulation. Results are compared with previous study of rebinding dynamics at 300 K in water in order to understand how the change of protein environment and the underlying protein energy landscape influence the dynamics. Rebinding dynamics at 77, 180, and 300 K exhibits changes in both time scale and mechanism as the protein and solvent undergo a dynamic "glass transition".

On the pH Dependent Behavior of the Firefly Bioluminescence: Protein Dynamics and Water Content in the Active Pocket

Hyun Woo Kim and Young Min Rhee [Pohang University of Science and Technology (POSTECH),]

J. Phys. Chem. B., **117**, 7260–7269, 2013**.**

Understanding bioluminescence presents fascinating challenges for fundamental sciences and numerous opportunities for practical applications. As a representative example, the firefly bioluminescent system has been intensively studied in both experimental and computational areas. However, there are still remaining questions regarding especially the detailed protein dynamics and the mechanisms of its color modulation. Here, we report on the pH dependent behavior of the firefly bioluminescence primarily based on molecular dynamics simulations. We find that the overall protein structure is generally resilient to pH variations.

Aggregation Thermodynamics of Sodium Octanoate Micelles Studied by Means of Molecular Dynamics Simulations

Kalil Bernardino and André F. de Moura [Universidade Federal de São Carlos,]

J. Phys. Chem. B., **117**, 7324–7334, 2013**.**

The present work is aimed at studying the computation of the thermodynamic potentials that describe the stability of anionic surfactant molecules in micellar aggregates. We report a set of molecular dynamics simulations of a sodium octanoate micelle in aqueous solution using the umbrella sampling method along with the Jarzynski equality in order to compute the potential of mean force for the dissociation process of one surfactant molecule from a previously assembled micellar aggregate. The Jarzynski average was computed at several different temperatures in order to estimate the Gibbs energy of association for the octanoate anion, which was split into its enthalpic and entropic contributions.

Protein Dynamics (Cont'd)

Molecular Dynamics Simulation of the Arginine-Assisted Solubilization of Caffeic Acid: Intervention in the Interaction

Atsushi Hirano , Tomoshi Kameda , Daisuke Shinozaki , Tsutomu Arakawa , and Kentaro Shiraki [University of Tsukuba,]

J. Phys. Chem. B., **117**, 7518–7527, 2013**.**

We have previously demonstrated that arginine increases the solubility of aromatic compounds that have poor water solubility, an effect referred to as the "arginine-assisted solubilization system (AASS)". In the current study, we utilized a molecular dynamics simulation to examine the solubilization effects of arginine on caffeic acid, which has a tendency to aggregate in aqueous solution. Caffeic acid has a hydrophobic moiety containing a π-conjugated system that includes an aromatic ring and a hydrophilic moiety with hydroxyl groups and a carboxyl group.

Car–Parrinello Molecular Dynamics/Molecular Mechanics (CPMD/MM) Simulation Study of Coupling and Uncoupling Mechanisms of Cytochrome P450cam

Peng Lian , Jue Li , Dong-Qi Wang , and Dong-Qing Wei [Shanghai Jiao Tong University,]

J. Phys. Chem. B., **117**, 7849–7856, 2013**.**

The relevance of the pathway through which the second proton is delivered to the active site of P450cam and the subsequent coupling/uncoupling reactions has been investigated using Car–Parrinello molecular dynamics/molecular mechanics (CPMD/MM) dynamics simulations. Five models have been prepared, representing delivery pathways in the wild-type enzyme and its mutants in which Thr252 mutated into other residues with different side-chain length and hydrophobicity.

Molecular Details of the Activation of the μ Opioid Receptor

Jihyun Shim, Andrew Coop, and Alexander D. MacKerell, Jr. [University of Maryland School of Pharmacy]

J. Phys. Chem. B., **117**, 7907–7917, 2013**.**

Molecular details of μ opioid receptor activations were obtained using molecular dynamics simulations of the receptor in the presence of three agonists, three antagonists, and a partial agonist and on the constitutively active T279K mutant. Agonists have a higher probability of direct interactions of their basic nitrogen (N) with Asp147 as compared with antagonists, indicating that direct ligand–Asp147 interactions modulate activation.

Free Energy Profile and Mechanism of Self-Assembly of Peptide Amphiphiles Based on a Collective Assembly Coordinate

Tao Yu and George C. Schatz [Northwestern University,]

J. Phys. Chem. B., **117**, 9004–9013, 2013**.**

By combining targeted molecular dynamics (TMD) simulations, umbrella sampling, and the weighted histogram analysis method (WHAM), we have calculated the potential of mean force (PMF) for the transition between the bound and free states of 90 peptide amphiphiles (PAs) in aqueous solution, with the bound state corresponding to a cylindrical micelle fiber. We specifically consider a collective reaction coordinate, the radius of gyration of the PAs, to describe assembly in this work.

Protein Dynamics (Cont'd)

Reversal of the Hofmeister Series: Specific Ion Effects on Peptides

Jana Paterová, Kelvin B. Rembert, Jan Heyda, Yadagiri Kurra, Halil I. Okur, Wenshe R. Liu, Christian Hilty, Paul S. Cremer, and Pavel Jungwirth [Academy of Sciences of the Czech Republic,]

J. Phys. Chem. B., **117**, 8150–8158, 2013**.**

Ion-specific effects on salting-in and salting-out of proteins, protein denaturation, as well as enzymatic activity are typically rationalized in terms of the Hofmeister series. Here, we demonstrate by means of NMR spectroscopy and molecular dynamics simulations that the traditional explanation of the Hofmeister ordering of ions in terms of their bulk hydration properties is inadequate. Using triglycine as a model system, we show that the Hofmeister series for anions changes from a direct to a reversed series upon uncapping the N-terminus.

Insight into the Molecular Mechanisms of Protein Stabilizing Osmolytes from Global Force-Field Variations

Emanuel Schneck, Dominik Horinek, and Roland R. Netz [Freie Universität Berlin,]

J. Phys. Chem. B., **117**, 8310–8321, 2013**.**

A prominent class of osmolytes that are able to stabilize proteins in their native fold consist of small highly water-soluble molecules with a large dipole moment and hydrophobic groups attached to the positively charged end of the molecule, for which we coin the term dipolar/hydrophobic osmolytes. For TMAO, which is a prime member of this class, we perform large-scale water-explicit MD simulations and determine the bulk solution activity coefficient as well as the affinity to a stretched polyglycine chain for varying TMAO dipolar strength and hydrophobicity.

Trimethylamine-N-oxide's Effect on Polypeptide Solvation at High Pressure: A Molecular Dynamics Simulation Study

Rahul Sarma and Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **117**, 9056–9066, 2013**.**

The solvation characteristics of a 15-residue polypeptide and also the structure of the solution in the presence and absence of trimethylamine-N-oxide (TMAO), one of the strongest known protein stabilizers among the natural osmolytes both at low and high pressures, are investigated under high pressure conditions by employing the molecular dynamics simulation technique. The goal is to provide a molecular level understanding of how TMAO protects proteins at elevated pressures. Two different conformations of the polypeptide are used: helix and extended.

Dissipative Particle Dynamics Simulation of the Phase Behavior of T-Shaped Ternary Amphiphiles Possessing Rodlike Mesogens

Xiaohan Liu, Keda Yang, and Hongxia Guo [Chinese Academy of Sciences,]

J. Phys. Chem. B., **117**, 9106–9120, 2013**.**

We employed dissipative particle dynamics simulations to explore the phase behavior of T-shaped ternary amphiphiles composed of rodlike cores connected by two incompatible end chains and side grafted segments. By fine-tuning the number of terminal and lateral beads, three phase diagrams for the model systems with different terminal chain lengths are constructed in terms of temperature and lateral chain length, which have some common features and mostly compare favorably with experimental studies with the exception a couple of new phases.

Free Energy Calculations

Calculating the Sensitivity and Robustness of Binding Free Energy Calculations to Force Field Parameters

Gabriel J. Rocklin [University of California San Francisco], David L. Mobley, and Ken A. Dill

J. Chem. Theor. and Comp, **9**, 3072-3083, 2013.

Binding free energy calculations offer a thermodynamically rigorous method to compute protein–ligand binding, and they depend on empirical force fields with hundreds of parameters. We examined the sensitivity of computed binding free energies to the ligand's electrostatic and van der Waals parameters. Dielectric screening and cancellation of effects between ligand–protein and ligand–solvent interactions reduce the parameter sensitivity of binding affinity by 65%, compared with interaction strengths computed in the gas-phase.

Multisite Ion Models That Improve Coordination and Free Energy Calculations in Molecular Dynamics Simulations

Akansha Saxena and David Sept [University of Michigan]

J. Chem. Theor. and Comp, **9**, 3538–3542, 2013.

Current ion models in molecular mechanics are simple spheres, and their interactions are solely determined from the van der Waals radius of the sphere and the total charge. Here, we introduce a model where we distribute the total charge of the ion into n-dummy centers that are placed in the direction of the coordinating atoms. We have parametrized this model for two divalent cations, Ca2+ and Mg2+, and have tested the model's accuracy in a variety of simulations.

Ligand Binding/Docking

Binding affinity of substituted ureido-benzenesulfonamide ligands to the carbonic anhydrase receptor: A theoretical study of enzyme inhibition

Chandan Sahu, Kaushik Sen, Srimanta Pakhira, Bhaskar Mondal, Abhijit K. Das [Indian Association for the Cultivation of Science, Jadavpur,]

J. Comp. Chem., **34**, 1907–1916, 2013.

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The binding properties of a series of benzenesulfonamide inhibitors (4-substituted-ureido-benzenesulfonamides, UBSAs) of human carbonic anhydrase II (hCA II) enzyme with active site residues have been studied using a hybrid quantum mechanical/molecular mechanical (QM/MM) model. To account for the important docking interactions between the UBSAs ligand and hCA II enzyme, a molecular docking program AutoDock Vina is used. The molecular docking results obtained by AutoDock Vina revealed that the docked conformer has root mean square deviation value less than 1.50 Å compared to X-ray crystal structures.

Ligand Binding / Docking (Cont'd)

Interactions of acetylcholine binding site residues contributing to nicotinic acetylcholine receptor gating: Role of residues Y93, Y190, K145 and D200

Prema L. Mallipeddi, Steen E. Pedersen, James M. Briggs [University of Houston]

J. Mol.Graph. and Mod., **44,** 145–154, 2013.

The nicotinic acetylcholine receptor exhibits multiple conformational states, resting (channel closed), active (channel open) and desensitized (channel closed). The resting state may be distinguished from the active and desensitized states by the orientation of loop C in the extracellular ligand binding domain (LBD). Homology modeling was used to generate structures of the *Torpedo californica* $\alpha_2\beta\delta\gamma$ nAChR that initially represent the resting state (loop C open) and the desensitized state (loop C closed). Molecular dynamics (MD) simulations were performed on the extracellular LBD on each nAChR conformational state, with and without the agonist anabaseine present in each binding site (the $\alpha\gamma$ and the $\alpha\delta$ sites).

Molecular modeling revealed that ligand dissociation from thyroid hormone receptors is affected by receptor heterodimerization

Shulin Zhuang[Zhejiang University], Lingling Bao, Apichart Linhananta, Weiping Liu

J. Mol.Graph. and Mod., **44,** 155–160, 2013.

Numerous ligands bind tightly to thyroid hormone receptors (TRs), and exploring the binding and dissociation of these ligands from TRs will increase our understanding of their mechanisms of action. TRs form transcriptionally active heterodimers with retinoid X receptor (RXR); whether this heterodimerization affects ligand dissociation is poorly understood. To investigate the effects of heterodimerization, classical molecular dynamics (MD) simulations and random acceleration molecular dynamics (RAMD) simulations were performed to probe the dissociation of triiodothyronine (T3) from a TRα-RXR ligand binding domain (LBD) heterodimer and the TRα and TRβ LBDs at the atomic level.

***In silico* design: Extended molecular dynamic simulations of a new series of dually acting inhibitors against EGFR and HER2**

Marawan Ahmed, Maiada M. Sadek, Khaled A. Abouzid, Feng Wang[Swinburne University of Technology]

J. Mol.Graph. and Mod., **44,** 220–231, 2013.

Based on the hit structures that have been identified in our previous studies against EGFR and HER2, new potential inhibitors that share the same scaffold of the hit structures are designed and screened *in silico*. Insights into understanding the potential inhibitory effect of the new inhibitors against both EGFR and HER2 receptors is obtained using extended molecular dynamics (MD) simulations and different scoring techniques. The binding mechanisms and dynamics are detailed with respect to two approved inhibitors against EGFR (lapatinib) and HER2 (SYR127063).

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Ligand Binding / Docking (Cont'd)

Insight into the binding model of new antagonists of kappa receptor using docking and molecular dynamics simulation

Shiyuan Hu, Haijing Yu, Yongjuan Liu, Tian Xue, Huabei Zhang [Beijing Normal University]

J. Mol.Mod., **19,** 3087-3094, 2013.

PF-4455242 and its analogues represent a new series of kappa opioid selective antagonists that demonstrate high selectivity and potency. We investigated their binding mode to the κ-receptor via docking and molecular dynamics simulations. The ranking of the predicted binding free energies is consistent with experimental results.

Metal ions in sugar binding, sugar specificity and structural stability of*Spatholobus parviflorus* seed lectin

Joseph Abhilash, Kalarickal Vijayan Dileep, Muthusamy Palanimuthu, Krishnan Geethanandan, Chittalakkotu Sadasivan, Madhathilkovilakath Haridas [Kannur University]

J. Mol.Mod., **19,** 3271-3278, 2013.

S!

Spatholobus parviflorus seed lectin (SPL) is a heterotetrameric lectin, with two α and two β monomers. In the crystal structure of SPL α monomer, two residues at positions 240 and 241 are missing. This region was modeled based on the positional and sequence similarities. The role of metal ions in SPL structure was analyzed by 10 ns molecular dynamics simulation. MD simulations were performed in the presence and absence of metal ions to explain the loss of haemagglutinating property of the lectin due to demetallization. Demetallized structure was found to deviate drastically at the metal binding loop region.

Investigation of the Noncovalent Binding Mode of Covalent Proteasome Inhibitors around the Transition State by Combined Use of Cyclopropylic Strain-Based Conformational Restriction and Computational Modeling

Shuhei Kawamura , Yuka Unno , Motohiro Tanaka , Takuma Sasaki , Akihito Yamano , Takatsugu Hirokawa , Tomoshi Kameda , Akira Asai, Mitsuhiro Arisawa, and Satoshi Shuto[Hokkaido University]

J.Med.Chem., **56,** 5829–5842, 2013.

To develop potent covalent inhibitors, the noncovalent interactions around the transition state to form covalent bonding should be optimized because the potency of the inhibitor can be depending on the energy of the transition state. Here, we report an efficient analysis of the noncovalent binding mode of a potent covalent proteasome inhibitor 3a around the transition state by a combined use of the chemical approach, i.e., the cyclopropylic strain-based conformational restriction, and the computational docking approach.

Chemical Genomics Approach for GPCR–Ligand Interaction Prediction and Extraction of Ligand Binding Determinants

Akira Shiraishi , Satoshi Niijima , J. B. Brown ,Masahiko Nakatsui , and Yasushi Okuno [Kyoto University]

J.Chem. Infor. and Mod. **53**, 1253–1262, 2013.

Chemical genomics research has revealed that G-protein coupled receptors (GPCRs) interact with a variety of ligands and that a large number of ligands are known to bind GPCRs even with low transmembrane (TM) sequence similarity. It is crucial to extract informative binding region propensities from large quantities of bioactivity data. To address this issue, we propose a machine learning approach that enables identification of both chemical substructures and amino acid properties that are associated with ligand binding, which can be applied to virtual ligand screening on a GPCR-wide scale.

Ligand Binding / Docking (Cont'd)

Computationally-predicted CB1 cannabinoid receptor mutants show distinct patterns of salt-bridges that correlate with their level of constitutive activity reflected in G protein coupling levels, thermal stability, and ligand binding

Kwang H. Ahn, Caitlin E. Scott, Ravinder Abrol, William A. Goddard III, Debra A. Kendall[University of Connecticut,]

Proteins: Stru. Fun. & Bioinf., **81**, 1304–1317, 2013.

The cannabinoid receptor 1 (CB1), a member of the class A G-protein-coupled receptor (GPCR) family, possesses an observable level of constitutive activity. Its activation mechanism, however, has yet to be elucidated. Previously we discovered dramatic changes in CB1 activity due to single mutations; T3.46A, which made the receptor inactive, and T3.46I and L3.43A, which made it essentially fully constitutively active. Our subsequent prediction of the structures of these mutant receptors indicated that these changes in activity are explained in terms of the pattern of salt-bridges in the receptor region involving transmembrane domains 2, 3, 5, and 6.

Theoretical investigation on the diatomic ligand migration process and ligand binding properties in non-O_2-binding H-NOX domain

Yuebin Zhan, Li Liu, Lei Wu,Shuai Li, Fei Li, Zhengqiang L [Jilin University,]

Proteins: Stru. Fun. & Bioinf., **81**, 1363–1376, 2013.

The *Nostoc sp* (*Ns*) H-NOX (heme-nitric oxide or OXygen-binding) domain shares 35% sequence identity with soluble guanylate cyclase (sGC) and exhibits similar ligand binding property with the sGC. Previously, our MD simulation work identified that there exists a Y-shaped tunnel system hosted in the *Ns* H-NOX interior, which servers for ligand migration. In this work, to further investigate how the protein matrix of *Ns* H-NOX modulates the ligand migration process and how the distal residue composition affects the ligand binding prosperities, the free energy profiles for nitric oxide, carbon monooxide, and O_2 migration are explored using the steered MDs simulation and the ligand binding energies are calculated using QM/MM schemes.

Liquid–Liquid Extraction of Uranyl by an Amide Ligand: Interfacial Features Studied by MD and PMF Simulations

G. Benay and G. Wipff [Laboratoire MSM]

J. Phys. Chem. B., **117**, 7399–7415, 2013**.**

We report a molecular dynamics study of biphasic systems involved in the liquid–liquid extraction of uranyl nitrate by a monoamide ligand (L = N,N-di(2-ethylhexyl)isobutyramide, DEHiBA) to hexane, from pH neutral or acidic (3 M nitric acid) aqueous solutions. We first describe the neat interfaces simulated with three electrostatic models, one of which including atomic polarizabilities. The free energy profiles for crossing the water/hexane interface by L or its UO2(NO3)2L2 complex are then investigated by PMF (potential of mean force) calculations. They indicate that the free ligand and its complex are surface active.

Carbohydrate–Aromatic Interactions: Vibrational Spectroscopy and Structural Assignment of Isolated Monosaccharide Complexes with p-Hydroxy Toluene and N-Acetyl l-Tyrosine Methylamide

E. Cristina Stanca-Kaposta, Pierre Çarçabal, Emilio J. Cocinero, Paola Hurtado, and John P. Simons [University of Oxford,]

J. Phys. Chem. B., **117**, 8135–8142, 2013**.**

The nature of carbohydrate binding first to p-hydroxy toluene and then the capped amino acid, N-acetyl L-tyrosine methyl amide (AcTyrNHMe), has been investigated in a solvent-free environment under molecular beam conditions. A combination of double resonance IR-UV spectroscopy and quantum chemical calculations has established the structures of complexes with the α and β anomers of methyl D-gluco- and D-galacto- and L-fucopyranosides (α/βMeGlc, MeGal, MeFuc).

Ligand Binding / Docking (Cont'd)

Quantum and All-Atom Molecular Dynamics Simulations of Protonation and Divalent Ion Binding to Phosphatidylinositol 4,5-Bisphosphate (PIP2)

David R. Slochower , Peter J. Huwe , Ravi Radhakrishnan , and Paul A. Janmey [University of Pennsylvania,]

J. Phys. Chem. B., **117**, 8322–8329, 2013**.**

Molecular dynamics calculations have been used to determine the structure of phosphatidylinositol 4,5 bisphosphate (PIP2) at the quantum level and to quantify the propensity for PIP2 to bind two physiologically relevant divalent cations, Mg2+ and Ca2+. We performed a geometry optimization at the Hartree–Fock 6-31+G (d) level of theory in vacuum and with a polarized continuum dielectric to determine the conformation of the phospholipid headgroup in the presence of water and its partial charge distribution.

Enzyme Catalysis

Molecular modeling, dynamics, and an insight into the structural inhibition of cofactor independent phosphoglycerate mutase isoform 1 from *Wuchereria bancrofti* using cheminformatics and mutational studies

Om Prakash Sharma[a], Yellamandayya Vadlamudi[a],Qinghua Liao[b], Birgit Strodel[b] & Muthuvel Suresh Kumar [Pondicherry University]

J. Biomol. Stru. and Dyn., ***31***, 765-778, *2013.*

Phosphoglycerate mutase catalyzes the interconversion between 2-phosphoglycerate and 3-phosphoglycerate in the glycolytic and gluconeogenic pathways. They exist in two unrelated forms, that is either cofactor (2,3-diphosphoglycerate) dependent or cofactor-independent. These two enzymes have no similarity in amino acid sequence, tertiary structure, and in catalytic mechanism. In this current study, a putative cofactor-iPGM gene was identified in the protein sequence of the WB. In the absence of crystal structure, a three-dimensional structure was determined using the homology modeling approximation.

Synthesis and biological evaluation of cationic fullerene quinazolinone conjugates and their binding mode with modeled *Mycobacterium tuberculosis*hypoxanthine-guanine phosphoribosyltransferase enzyme

Manishkumar B. Patel, Sivakumar Prasanth Kumar, Nikunj N. Valand, Yogesh T. Jasrai, Shobhana K. Menon[Gujarat University,]

J. Mol.Mod., **19,** 3201-3217, 2013.

The present work reports a series of novel cationic fullerene derivatives bearing a substituted-quinazolinone moiety as a side arm. Fullerene-quinazolinone conjugates synthesized using the 1,3-dipolar cycloaddition reaction of C_{60} with azomethine ylides generated from the corresponding Schiff bases of substituted quinazolinone were characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and ESI-MS and screened for their antibacterial activity against *Mycobacterium tuberculosis* (*H_{37}Rv* strain).

Effect of Halogen Substitutions on dUMP to Stability of Thymidylate Synthase/dUMP/mTHF Ternary Complex Using Molecular Dynamics Simulation

Nopporn Kaiyawet , Thanyada Rungrotmongkol , and Supot Hannongbua [Chulalongkorn University,]

J.Chem. Infor. and Mod. **53**, 1315–1323, 2013.

The stability of the thymidylate synthase (TS)/2-deoxyuridine-5-monophosphate (dUMP)/5,10-methylene-5,6,7,8-tetrahydrofolate (mTHF) ternary complex formation and Michael addition are considered as important steps that are involved in the inhibition mechanism of the anticancer prodrug 5-fluorouracil (5-FU). Here, the effect of three different halogen substitutions on the C-5 position of the dUMP (XdUMPs = FdUMP, CldUMP, and BrdUMP), the normal substrate, on the stability of the TS/dUMP and TS/dUMP/mTHF binary and ternary complexes, respectively, was investigated via MD simulation.

Enzyme Catalysis (Cont'd)

Clarification on the Decarboxylation Mechanism in KasA Based on the Protonation State of Key Residues in the Acyl-Enzyme State

Wook Lee and Bernd Engels [Universität Würzburg]

J. Phys. Chem. B., **117**, 8095-8104, 2013**.**

The β-ketoacyl ACP synthase I (KasA) is a promising drug target because it is essential for the survival of Mycobacterium tuberculosis, a causative agent of tuberculosis. It catalyzes a condensation reaction that comprises three steps. In this first computational study about this topic, we use the free energy perturbation (FEP) method to compute the relevant pKa values in the acyl-enzyme state of KasA and use MD simulations to rationalize the results.

Concerted Hydrogen Atom and Electron Transfer Mechanism for Catalysis by Lysine-Specific Demethylase

Tao Yu, Masahiro Higashi, Alessandro Cembran, Jiali Gao, and Donald G. Truhlar [University of Minnesota]

J. Phys. Chem. B., **117**, 8422–8429, 2013**.**

We calculate the free energy profile for the postulated hydride transfer reaction mechanism for the catalysis of lysine demethylation by lysine-specific demethylase LSD1. The potential energy surface is obtained by using combined electrostatically embedded multiconfiguration molecular mechanics (EE-MCMM) and single-configuration molecular mechanics (MM).

Factors That Drive Peptide Assembly and Fibril Formation: Experimental and Theoretical Analysis of Sup35 NNQQNY Mutants

Thanh D. Do, Nicholas J. Economou, Nichole E. LaPointe, William M. Kincannon, Christian Bleiholder, Stuart C. Feinstein, David B. Teplow, Steven K. Buratto, and Michael T. Bowers [University of California]

J. Phys. Chem. B., **117**, 8436–8446, 2013**.**

Residue mutations have substantial effects on aggregation kinetics and propensities of amyloid peptides and their aggregate morphologies. Such effects are attributed to conformational transitions accessed by various types of oligomers such as steric zipper or single β-sheet. We have studied the aggregation propensities of six NNQQNY mutants: NVVVVY, NNVVNV, NNVVNY, VIQVVY, NVVQIY, and NVQVVY in water using a combination of ion-mobility mass spectrometry, transmission electron microscopy, atomic force microscopy, and all-atom molecular dynamics simulations.

Protein-Protein Interactions

NETAL: a new graph-based method for global alignment of protein–protein interaction networks

Behnam Neyshabur ,Ahmadreza Khadem ,Somaye Hashemifar and Seyed Shahriar Arab [University of Tehran]

Bioinformatics. **29**, 1654-1662, 2013.

The interactions among proteins and the resulting networks of such interactions have a central role in cell biology. Aligning these networks gives us important information, such as conserved complexes and evolutionary relationships. Although there have been several publications on the global alignment of protein networks; however, none of proposed methods are able to produce a highly conserved and meaningful alignment. We present a novel algorithm for the global alignment of protein–protein interaction networks.

Protein-Protein Interactions (Cont'd)

pyDockWEB: a web server for rigid-body protein–protein docking using electrostatics and desolvation scoring

Brian Jiménez-García, Carles Pons and Juan Fernández-Recio [National Institute of Bioinformatics (INB)]

Bioinformatics. **29**, 1698-1699, 2013.

pyDockWEB is a web server for the rigid-body docking prediction of protein–protein complex structures using a new version of the pyDock scoring algorithm. We use here a new custom parallel FTDock implementation, with adjusted grid size for optimal FFT calculations, and a new version of pyDock, which dramatically speeds up calculations while keeping the same predictive accuracy. Given the 3D coordinates of two interacting proteins, pyDockWEB returns the best docking orientations as scored mainly by electrostatics and desolvation energy.

Protein–Protein Interaction Regulates the Direction of Catalysis and Electron Transfer in a Redox Enzyme Complex

Duncan G. G. McMillan , Sophie J. Marritt ,Mackenzie A. Firer-Sherwood , Liang Shi , David J. Richardson , Stephen D. Evans , Sean J. Elliott , Julea N. Butt , and Lars J. C. Jeuken [University of Leeds,]

J. Am. Chem. Soc., 2013, **135**, 10550–10556

Protein–protein interactions are well-known to regulate enzyme activity in cell signaling and metabolism. Here, we show that protein–protein interactions regulate the activity of a respiratory-chain enzyme, CymA, by changing the direction or bias of catalysis. CymA, a member of the widespread NapC/NirT superfamily, is a menaquinol-7 (MQ-7) dehydrogenase that donates electrons to several distinct terminal reductases in the versatile respiratory network of Shewanella oneidensis. We report the incorporation of CymA within solid-supported membranes that mimic the inner membrane architecture of S. oneidensis.

Identification of M. tuberculosis Thioredoxin Reductase Inhibitors Based on High-Throughput Docking Using Constraints

Oliver Koch [MSD Animal Health Innovation GmbH] , Timo Jäger , Kristin Heller ,Purushothama Chary Khandavalli , Jette Pretzel ,Katja Becker , Leopold Flohé , and Paul M. Selzer

J.Med.Chem., **56,** 4849–4859, 2013.

A virtual screening campaign is presented that led to small molecule inhibitors of thioredoxin reductase of Mycobacterium tuberculosis (MtTrxR) that target the protein–protein interaction site for the substrate thioredoxin (Trx). MtTrxR is a promising drug target because it dominates the Trx-dependent hydroperoxide metabolism and the reduction of ribonucleotides, thus facilitating survival and proliferation of M. tuberculosis

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Intermolecular Contact Potentials for Protein–Protein Interactions Extracted from Binding Free Energy Changes upon Mutation

Iain H. Moal and Juan Fernandez-Recio [Barcelona Supercomputing Center,]

J. Chem. Theor. and Comp, **9**, 3715–3727, 2013.

Understanding and predicting the energetics of protein–protein interactions is fundamental to the structural modeling of protein complexes. Binding free energy can be approximated as a sum of pairwise atomic or residue contact energies, which are commonly inferred from contact frequencies observed in experimental protein structures. However, such statistically inferred potentials require certain assumptions and approximation. Here, we explore the possibility of deriving atomic and residue contact potentials directly from experimental binding free energy changes following mutation and present a number of such potentials

Protein-Protein Interactions (Cont'd)

Efficient Determination of Protein–Protein Standard Binding Free Energies from First Principles

James C. Gumbart, Benoît Roux, and Christophe Chipot [University of Illinois at Urbana−Champaign,]

J. Chem. Theor. and Comp, **9**, 3789–3798, 2013.

Characterizing protein–protein association quantitatively has been a long standing challenge for computer simulations. Here, a theoretical framework is put forth that addresses this challenge on the basis of detailed all-atom molecular dynamics simulations with explicit solvent. The proposed methodology relies upon independent potential of mean force (PMF) free-energy calculations carried out sequentially, wherein the biological objects are restrained in the conformation, position, and orientation of the bound state, using adequately chosen biasing potentials.

Membrane Proteins and Lipid Peptide Interactions

Nonfitting protein–ligand interaction scoring function based on first-principles theoretical chemistry methods: Development and application on kinase inhibitors

Li Rao, Igor Ying Zhang, Wenping Guo, Li Feng, Eric Meggers, Xin Xu [Philipps-University Marburg]

J. Comp. Chem., **34**, 1636–1646, 2013.

Targeted therapy is currently a hot topic in the fields of cancer research and drug design. An important requirement for this approach is the development of potent and selective inhibitors for the identified target protein. However, current ways to estimate inhibitor efficacy rely on empirical protein–ligand interaction scoring functions which, suffering from their heavy parameterizations, often lead to a low accuracy. In this work, we develop a nonfitting scoring function.

Improving the Scoring of Protein–Ligand Binding Affinity by Including the Effects of Structural Water and Electronic Polarization

Jinfeng Liu , Xiao He, and John Z. H. Zhang [East China Normal University,]

J.Chem. Infor. and Mod. **53**, 1306–1314, 2013.

The polarized protein-specific charge model (PPC) is incorporated into the molecular mechanics/Poisson–Boltzmann surface area (MM/PBSA) method to rescore the binding poses of some protein–ligand complexes, for which docking programs, such as Autodock, could not predict their binding modes correctly. Different sampling techniques (single minimized conformation and multiple molecular dynamics (MD) snapshots) are used to test the performance of MM/PBSA combined with the PPC model.

Lennard-Jones Lattice Summation in Bilayer Simulations Has Critical Effects on Surface Tension and Lipid Properties

Christian L. Wennberg, Teemu Murtola, Berk Hess, and Erik Lindahl [Stockholm University]

J. Chem. Theor. and Comp, **9**, 3527–3537, 2013.

The accuracy of electrostatic interactions in molecular dynamics advanced tremendously with the introduction of particle-mesh Ewald (PME) summation almost 20 years ago. Lattice summation electrostatics is now the de facto standard for most types of biomolecular simulations, and in particular, for lipid bilayers. In contrast, Lennard-Jones interactions have continued to be handled with increasingly longer cutoffs, partly because few alternatives have been available despite significant difficulties in tuning cutoffs and parameters to reproduce lipid properties. Here, we present a new Lennard-Jones PME implementation applied to lipid bilayers.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Accelerating Convergence in Molecular Dynamics Simulations of Solutes in Lipid Membranes by Conducting a Random Walk along the Bilayer Normal

Chris Neale, Chris Madill, Sarah Rauscher, and Régis Pomès [University of Toronto,]

J. Chem. Theor. and Comp, **9**, 3686–3703, 2013.

All MD simulations are susceptible to sampling errors, which degrade the accuracy and precision of observed values. The statistical convergence of simulations containing atomistic lipid bilayers is limited by the slow relaxation of the lipid phase, which can exceed hundreds of nanoseconds. These long conformational autocorrelation times are exacerbated in the presence of charged solutes, which can induce significant distortions of the bilayer structure. To identify optimal methods for enhancing sampling efficiency, we quantitatively evaluate convergence rates using generalized ensemble sampling algorithms in calculations of the potential of mean force for the insertion of the ionic side chain analog of arginine in a lipid bilayer.

Role of the Membrane Dipole Potential for Proton Transport in Gramicidin A Embedded in a DMPC Bilayer

Jens Dreyer, Chao Zhang, Emiliano Ippoliti, and Paolo Carloni [Joint venture of RWTH Aachen University and Forschungszentrum Jülich,]

J. Chem. Theor. and Comp, **9**, 3826–3831, 2013.

The membrane potential at the water/phospholipid interfaces may play a key role for proton conduction of gramicidin A (gA). Here we address this issue by DFT-based molecular dynamics and metadynamics simulations. The calculations, performed on gA embedded in a solvated 1,2-dimyristoyl-sn-glycero-3-phosphocholine model membrane environment, indicate that (i) the membrane dipole potential rises at the channel mouth by 0.4 V. A similar value has been measured for gA embedded in a DMPC monolayer; (ii) the calculated free energy barrier is located at the channel entrance, consistent with experiments comparing gA proton conduction in different bilayers.

Comparison of Molecular Mechanics, Semi-Empirical Quantum Mechanical, and Density Functional Theory Methods for Scoring Protein–Ligand Interactions

Nusret Duygu Yilmazer and Martin Korth [Ulm University]

J. Phys. Chem. B., **117**, 8075-8084, 2013**.**

Correctly ranking protein–ligand interactions with respect to overall free energy of binding is a grand challenge for virtual drug design. Here we compare the performance of various quantum chemical approaches for tackling this so-called "scoring" problem. Relying on systematically generated benchmark sets of large protein/ligand model complexes based on the PDBbind database, we show that the performance depends first of all on the general level of theory.

Binding and Aggregation Mechanism of Amyloid β-Peptides onto the GM1 Ganglioside-Containing Lipid Membrane

Tyuji Hoshino [Chiba University,], Md. Iqbal Mahmood, Kenichi Mori, and Katsumi Matsuzaki

J. Phys. Chem. B., **117**, 8085–8094, 2013**.**

Accumulation and fibril formation of amyloid β (Aβ) peptides onto a ganglioside-rich lipid membrane is a cause of neuro-disturbance diseases. To find out a measure for suppressing the nucleation of a seed for amyloid fibrils, the mechanism of the initial binding of Aβ to the membrane should be clarified. MD simulations were carried out to investigate the adhesion process of Aβ peptides onto a GM1-ganglioside-containing membrane. Multiple computational trials were executed to analyze the probability of occurrence of Aβ binding by using calculation models containing a mixed lipid membrane, water layer, and one, two, or three Aβs.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Effects of Flanking Loops on Membrane Insertion of Transmembrane Helices: A Role for Peptide Conformational Equilibrium

Jian Gao and Jianhan Chen [Kansas State University,]

J. Phys. Chem. B., **117**, 8330–8339, 2013**.**

The ability of a transmembrane helix (TMH) to insert into a lipid bilayer has been mainly understood based on the total hydrophobicity of the peptide sequence. Recently, Hedin et al. investigated the influence of flanking loops on membrane insertion of a set of marginally hydrophobic TMHs using translocon-based membrane integration assays. Here, coarse-grained free energy calculations and atomistic simulations were performed to investigate the energetics and conformational details of the membrane insertion of two representative marginally hydrophobic TMHs with (NhaL and EmrL) and without (NhaA and EmrD) the flanking loops.

Comparative Computer Simulation Study of Cholesterol in Hydrated Unary and Binary Lipid Bilayers and in an Anhydrous Crystal

Elzbieta Plesnar , Witold K. Subczynski, and Marta Pasenkiewicz-Gierula [Jagiellonian University,]

J. Phys. Chem. B., **117**, 8758–8769 2013**.**

Models created with molecular dynamics simulations are used to compare the organization and dynamics of cholesterol (Chol) molecules in three different environments: (1) a hydrated pure Chol bilayer that models the Chol bilayer domain, which is a pure Chol domain embedded in the bulk membrane; (2) a 2-palmitoyl-3-oleoyl-D-glycerol-1-phosphorylcholine bilayer saturated with cholesterol (POPC-Chol50) that models the bulk membrane; (3) a Chol crystal. The computer model of the hydrated pure Chol bilayer is stable on the microsecond time scale.

A Polarizable Force Field of Dipalmitoylphosphatidylcholine Based on the Classical Drude Model for Molecular Dynamics Simulations of Lipids

Janamejaya Chowdhary, Edward Harder, Pedro E. M. Lopes, Lei Huang, Alexander D. MacKerell, Jr., and Benoît Roux [University of Chicago]

J. Phys. Chem. B., **117**, 9142–9160, 2013**.**

A polarizable force field of saturated phosphatidylcholine-containing lipids based on the classical Drude oscillator model is optimized and used in molecular dynamics simulations of bilayer and monolayer membranes. The hierarchical parametrization strategy involves the optimization of parameters for small molecules representative of lipid functional groups, followed by their application in larger model compounds and full lipids. The polar headgroup is based on molecular ions tetramethyl ammonium and dimethyl phosphate, the esterified glycerol backbone is based on methyl acetate, and the aliphatic lipid hydrocarbon tails are based on linear alkanes.

Protein Folding

Reconstructing the Most Probable Folding Transition Path from Replica Exchange Molecular Dynamics Simulations

Camilo Andres Jimenez-Cruz and Angel E. Garcia [Rensselaer Polytechnic Institute]

J. Chem. Theor. and Comp, **9**, 3750–3755, 2013.

In this work we demonstrate how the most probable transition path between metastable states can be recovered from replica exchange MD simulation data by using the dynamic string method. The local drift vector in collective variables is determined via short continuous trajectories between replica exchanges at a given temperature, and points along the string are updated based on this drift vector to produce reaction pathways between the folded and unfolded state. The method is applied to a designed beta hairpin-forming peptide to obtain information on the folding mechanism and transition state using different sets of collective variables at various temperatures.

Quantification of Drive-Response Relationships Between Residues During Protein Folding

Yifei Qi and Wonpil Im [The University of Kansas,]

J. Chem. Theor. and Comp, **9**, 3799–3805, 2013.

Mutual correlation and cooperativity are commonly used to describe residue–residue interactions in protein folding/function. Such drive-response relationships are poorly studied in protein folding/function and difficult to measure experimentally due to technical limitations. In this study, using the information theory transfer entropy (TE) that provides a direct measurement of causality between two times series, we have quantified the drive-response relationships between residues in the folding/unfolding processes of four small proteins generated by MD simulations.

Sampling of Protein Folding Transitions: Multicanonical Versus Replica Exchange Molecular Dynamics

Ping Jiang [University of Oklahoma], Fatih Yaşar, and Ulrich H. E. Hansmann

J. Chem. Theor. and Comp, **9**, 3816–3825, 2013.

We compare the efficiency of multicanonical and replica exchange molecular dynamics for the sampling of folding/unfolding events in simulations of proteins with end-to-end β-sheet. In Go-model simulations of the 75-residue MNK6, we observe improvement factors of 30 in the number of folding/unfolding events of multicanonical molecular dynamics over replica exchange molecular dynamics. As an application, we use this enhanced sampling to study the folding landscape of the 36-residue DS119 with an all-atom physical force field and implicit solvent.

Incorporating into a Cα Go model the effects of geometrical restriction on Cα atoms caused by side chain orientations

Masatake Sugita and Takeshi Kikuchi [Ritsumeikan University,]

Proteins: Stru. Fun. & Bioinf., **81**, 1434–1445, 2013.

Coarse-grained Go models have been widely used for studying protein-folding mechanisms. Despite the simplicity of the model, these can reproduce the essential features of the folding process of a protein. However, it is also known that side chains significantly contribute to the folding mechanism. Hence, it is desirable to incorporate the side chain effects into a coarse-grained Go model. In this study, to distinguish the effects of side chain orientation and to understand how these effects contribute to folding mechanisms, we incorporate into a Cα Go model not only heterogeneous contact energies but also geometrical restraints around two Cα atoms in contact with each other.

Protein Folding (Cont'd)

Folding of Top7 in unbiased all-atom Monte Carlo simulations

Sandipan Mohanty [Forschungszentrum Jülich], Jan H. Meinke, Olav Zimmermann

Proteins: Stru. Fun. & Bioinf., **81**, 1446–1456, 2013.

For computational studies of protein folding, proteins with both helical and β-sheet secondary structure elements are very challenging, as they expose subtle biases of the physical models. Here, we present reproducible folding of a 92 residue α/β protein (residues 3–94 of Top7, PDB ID: 1QYS) in computer simulations starting from random initial conformations using a transferable physical model which has been previously shown to describe the folding and thermodynamic properties of about 20 other smaller proteins of different folds. Top7 is a de novo designed protein with two α-helices and a five stranded β-sheet.

Protein-Nucleic acid Interactions

Preorientation of protein and RNA just before contacting

Dachuan Guo, Shiyong Liu, Yangyu Huang & Yi Xiao[Huazhong University of Science and Technology]

*J. Biomol. Stru. and Dyn., **31**,* 716-728, *2013.*

Protein and RNA molecules interact and form complexes in many biological processes. However, it is still unclear how they can find the correct docking direction before forming complex. In this paper, we study preorientation of RNA and protein separated at a distance of 5–7 Å just before they form contacts and interact with each other only through pure electrostatic interaction when neglecting the influence of other molecules and complicated environment.

Study on the interactions between diketo-acid inhibitors and prototype foamy virus integrase-DNA complex via molecular docking and comparative molecular dynamics simulation methods

Jian-Ping Hu, Hong-Qiu He, Dian-Yong Tang, Guo-Feng Sun, Yuan-Qin Zhang, Jing Fan & Shan Chang [South China Agricultural University ,]

*J. Biomol. Stru. and Dyn., **31**,* 734-747, *2013.*

Human immunodeficiency virus type 1 (HIV-1) integrase (IN) is an important drug target for anti-acquired immune deficiency disease (AIDS) treatment and diketo-acid (DKA) inhibitors are potent and selective inhibitors of HIV-1 IN. In addition, the action mechanism of DKA inhibitors with HIV-1 IN is not well understood. In view of the high homology between the structure of prototype foamy virus (PFV) IN and that of HIV-1 IN, we used PFV IN as a surrogate model for HIV-1 IN to investigate the inhibitory mechanism of raltegravir (RLV) and the binding modes with a series of DKA inhibitors.

Complex between *Human* RNase HI and the phosphonate-DNA/RNA duplex: Molecular dynamics study

Kamil Maláč , Ivan Barvík[Charles University]

J. Mol.Graph. and Mod., **44,** 81–90, 2013.

Our 200 ns MD simulations show that even fully modified oligonucleotides bearing the 3′-O-P-CH_2-O-5′ (but not 3′-O-CH_2-P-O-5′) phosphonate linkages can be successfully attached to the surface of *Human* RNase H. It enables to explain that oligonucleotides consisting of the alternating 3′-O-P-CH_2-O-5′ phosphonate and phosphodiester linkages are capable to elicit the RNase H activity (while the 3′-O-CH_2-P-O-5′ phosphonates are completely inactive).

Protein – Nucleic Acid Interactions (Cont'd)

Assessment of the photosensitization properties of cationic porphyrins in interaction with DNA nucleotide pairs

Gloria I. Cárdenas-Jirón [Universidad de Santiago de Chile (USACH),], Luis Cortez

J. Mol.Mod., **19,** 2913-2924, 2013.

We present a theoretical assessment of the photosensitization properties of meso-mono(N-methylpyridyl) triphenylporphyrin (1, MmPyP+), which interacts with DNA nucleotide pairs [adenine (A)-thymine (T); guanine (G)-cytosine (C)] via an external binding mode. The photosensitization properties of the arrangements 1A, 1T, 1G and 1C were investigated. A set of density functionals (B3LYP, PBE0, CAM-B3LYP, M06-2X, B97D) with the 6-31G(d) basis set was used to calculate the electronic absorption spectra in solution (water) following TD-DFT methodology.

Thermodynamic computational approach to capture molecular recognition in the binding of different inhibitors to the DNA gyrase B subunit from *Escherichia coli*

Liane Saíz-Urra, Miguel Ángel Cabrera Pérez, Matheus Froeyen [Katholieke Universiteit Leuven]

J. Mol.Mod., **19,** 3187-3200, 2013.

DNA gyrase subunit B, that catalyzes the hydrolysis of ATP, is an attractive target for the development of antibacterial drugs. This work is intended to rationalize molecular recognition at DNA gyrase B enzyme – inhibitor binding interface through the evaluation of different scoring functions in finding the correct pose and scoring properly 50 *Escherichia coli* DNA Gyrase B inhibitors belonging to five different classes.

Structural Role of Uracil DNA Glycosylase for the Recognition of Uracil in DNA Duplexes. Clues from Atomistic Simulations

Duvan Franco , Jacopo Sgrignani , Giovanni Bussi, and Alessandra Magistrato

J.Chem. Infor. and Mod. **53**, 1371–1387, 2013.

In the first stage of the base excision repair pathway the enzyme uracil DNA glycosylase (UNG) recognizes and excises uracil (U) from DNA filaments. U repair is believed to occur via a multistep base-flipping process, through which the damaged U base is initially detected and then engulfed into the enzyme active site, where it is cleaved. . Here, we performed force-field based molecular dynamics (MD) simulations to explore the structural and dynamical properties of distinct UNG/dsDNA adducts, containing A:U, A:T, G:U, or G:C base pairs, at different stages of the base-flipping pathway.

Probing the role of interfacial waters in protein–DNA recognition using a hybrid implicit/explicit solvation model

Shen Li and Philip Bradley[Fred Hutchinson Cancer Research Center,]

Proteins: Stru. Fun. & Bioinf., **81**, 1318–1329, 2013.

When proteins bind to their DNA target sites, ordered water molecules are often present at the protein–DNA interface bridging protein and DNA through hydrogen bonds. What is the role of these ordered interfacial waters? Are they important determinants of the specificity of DNA sequence recognition, or do they act in binding in a primarily nonspecific manner, by improving packing of the interface, shielding unfavorable electrostatic interactions, and solvating unsatisfied polar groups that are inaccessible to bulk solvent. We have developed a hybrid implicit/explicit solvation model that specifically accounts for the locations and orientations of small numbers of DNA-bound water molecules, while treating the majority of the solvent implicitly.

Protein – Nucleic Acid Interactions (Cont'd)

Dissociation Free-Energy Profiles of Specific and Nonspecific DNA–Protein Complexes

Yoshiteru Yonetani and Hidetoshi Kono [Japan Atomic Energy Agency,]

J. Phys. Chem. B., **117**, 7535–7545, 2013**.**

DNA-binding proteins recognize DNA sequences with at least two different binding modes: specific and nonspecific. Experimental structures of such complexes provide us a static view of the bindings. However, it is difficult to reveal further mechanisms of their target-site search and recognition only from static information because the transition process between the bound and unbound states is not clarified by static information. What is the difference between specific and nonspecific bindings? Here we performed adaptive biasing force molecular dynamics simulations with the specific and nonspecific structures of DNA–Lac repressor complexes to investigate the dissociation process.

Nucleic Acids

DNA Computation in Mammalian Cells: MicroRNA Logic Operations

James Hemphill and Alexander Deiters [North Carolina State University,]

J. Am. Chem. Soc., 2013, **135**, 10512–10518

DNA computation can utilize logic gates as modules to create molecular computers with biological inputs. Modular circuits that recognize nucleic acid inputs through strand hybridization activate computation cascades to produce controlled outputs. This allows for the construction of synthetic circuits that can be interfaced with cellular environments. We have engineered oligonucleotide AND gates to respond to specific microRNA (miRNA) inputs in live mammalian cells.

Intercalators as Molecular Chaperones in DNA Self-Assembly

Andrea A. Greschner, Katherine E. Bujold, and Hanadi F. Sleiman [McGill University]

J. Am. Chem. Soc., 2013, **135**, 11283–11288

DNA intercalation has found many diagnostic and therapeutic applications. Here, we propose the use of simple DNA intercalators, such as ethidium bromide, as tools to facilitate the error-free self-assembly of DNA nanostructures. We show that ethidium bromide can influence DNA self-assembly, decrease the formation of oligomeric side products, and cause libraries of multiple equilibrating structures to converge into a single product.

Influence of divalent magnesium ion on DNA: molecular dynamics simulation studies

Sanchita Mukherjee[a] & Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics ,]

*J. Biomol. Stru. and Dyn., **31**,* 896-912, *2013.*

A large amount of experimental evidence is available on the effect of magnesium ions on the structure and stability of DNA double helix. Less is known, however, on how these ions affect the stability and dynamics of the molecule. The static time average pictures from X-ray structures or the quantum chemical energy minimized structures lack understanding of the dynamic DNA–ion interaction. The present work addresses these questions by molecular dynamics simulation studies on two DNA duplexes and their interaction with magnesium ions. Results show typical B-DNA character with occasional excursions to deviated states.

Nucleic Acids (Cont'd)

Hidden Conformation Events in DNA Base Extrusions: A Generalized-Ensemble Path Optimization and Equilibrium Simulation Study

Liaoran Cao, Chao Lv, and Wei Yang [Florida State University,]

J. Chem. Theor. and Comp, **9**, 3756-3768, 2013.

DNA base extrusion is a crucial component of many biomolecular processes. Elucidating how bases are selectively extruded from the interiors of double-strand DNAs is pivotal to accurately understanding and efficiently sampling this general type of conformational transitions. In this work, the on-the-path random walk (OTPRW) method, which is the first generalized-ensemble sampling scheme designed for finite-temperature-string path optimizations, was improved and applied to obtain the minimum free-energy path (MFEP) and the free-energy profile of a classical B-DNA major-groove base-extrusion pathway. Along the MFEP, an intermediate state and the corresponding transition state were located and characterized.

Coarse-Grained Simulations of RNA and DNA Duplexes

Tristan Cragnolini, Philippe Derreumaux, and Samuela Pasquali [Université Paris Diderot,]

J. Phys. Chem. B., **117**, 8047–8060, 2013**.**

Although RNAs play many cellular functions, little is known about the dynamics and thermodynamics of these molecules. In principle, all-atom molecular dynamics simulations can investigate these issues, but with current computer facilities, these simulations have been limited to small RNAs and to short times. HiRe-RNA, a recently proposed high-resolution coarse-grained RNA that captures many geometric details such as base pairing and stacking, is able to fold RNA molecules to near-native structures in a short computational time. We present its application to duplexes of a couple dozen nucleotides and show how with replica exchange molecular dynamics.

Surfaces, Catalysts, and Materials Subjects

Immersion Depth of Surfactants at the Free Water Surface: A Computer Simulation and ITIM Analysis Study

Nóra Abrankó-Rideg, Mária Darvas, George Horvai, and Pál Jedlovszky [Eötvös Loránd University,]

J. Phys. Chem. B., **117**, 8733–8746, 2013**.**

The adsorption layer of five different surfactants, namely, pentanol, octanol, dodecanol, dodecyl trimethyl ammonium chloride, and sodium dodecyl sulfate, has been analyzed on the basis of molecular dynamics simulation results at two surface densities, namely, 1 and 4 μmol/m2. The analyses have primarily focused on the question of how deeply, in terms of atomistic layers, the different surfactant molecules are immersed into the aqueous phase. The orientation and conformation of the surfactant molecules have also been analyzed.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Beyond the Scope of Free-Wilson Analysis: Building Interpretable QSAR Models with Machine Learning Algorithms

Hongming Chen , Lars Carlsson , Mats Eriksson ,Peter Varkonyi , Ulf Norinder , and Ingemar Nilsson [Global Safety Assessment and CVGI Innovative Medicines,]

J.Chem. Infor. and Mod. **53**, 1324–1336, 2013.

A novel methodology was developed to build Free-Wilson like local QSAR models by combining R-group signatures and the SVM algorithm. Unlike Free-Wilson analysis this method is able to make predictions for compounds with R-groups not present in a training set. Eleven public data sets were chosen as test cases for comparing the performance of our new method with several other traditional modeling strategies, including Free-Wilson analysis. Our results show that the R-group signature SVM models achieve better prediction accuracy compared with Free-Wilson analysis in general.

X-ray Crystallographic Structures as a Source of Ligand Alignment in 3D-QSAR

Rafał D. Urniaż and Krzysztof Jóźwiak [Medical University of Lublin,]

J.Chem. Infor. and Mod. **53**, 1406–1414, 2013.

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Three-dimensional quantitative structure–activity relationships (3D-QSAR) analyses are methods correlating a pharmacological property with a mathematical representation of a molecular property distribution around three-dimensional molecular models for a set of congeners. 3D-QSAR methods are known to be highly sensitive to ligand conformation and alignment method. The current study collects 32 unique positions of congeneric ligands co-crystallized with the binding domain of AMPA receptors and aligns them using protein coordinates. Thus, it allows for a unique opportunity to consider a ligands' orientation aligned by their mode of binding in a native molecular target.

Quantum Mechanics-Based Properties for 3D-QSAR

Ahmed El Kerdawy, Stefan Güssregen, Hans Matter, Matthias Hennemann, and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg,]

J.Chem. Infor. and Mod. **53**, 1486–1502, 2013.

We have used a set of four local properties based on semiempirical molecular orbital calculations (electron density (ρ), hydrogen bond donor field (HDF), hydrogen bond acceptor field (HAF), and molecular lipophilicity potential (MLP)) for 3D-QSAR studies to overcome the limitations of the current force field-based molecular interaction fields (MIFs). These properties can be calculated rapidly and are thus amenable to high-throughput industrial applications.

Potentials and Parameters

A simple but effective modeling strategy for structural properties of non-heme Fe(II) sites in proteins: Test of force field models and application to proteins in the AlkB family

Xueqin Pang, Keli Han, Qiang Cui [University of Wisconsin]

J. Comp. Chem., **34**, 1620–1635, 2013.

To facilitate computational study of proteins in the AlkB family and related α-ketoglutarate/Fe(II)-dependent dioxygenases, we have tested a simple modeling strategy for the non-heme Fe(II) site in which the iron is represented by a simple +2 point charge with Lennard-Jones parameters. Calculations for an AlkB active site model in the gas phase and ~150 ns MD simulations for two enzyme-dsDNA complexes (E. coli AlkB-dsDNA and ABH2-dsDNA) suggest that this simple modeling strategy provides a satisfactory description of structural properties of the Fe(II) site in AlkB enzymes.

Cytochrome P450 compound I in the plane wave pseudopotential framework: GGA electronic and geometric structure of thiolate-ligated iron(IV)–oxo porphyrin

Justin E. Elenewski, John C Hackett [Virginia Commonwealth University]

J. Comp. Chem., **34**, 1647–1660 2, 2013.

The cytochromes P450 constitute a ubiquitous family of metalloenzymes, catalyzing manifold reactions of biological and synthetic importance via a thiolate-ligated iron-oxo (IV) porphyrin radical species denoted compound I (Cpd I). Experimental investigations have implicated this intermediate in a broad spectrum of biophysically interesting phenomena, further augmenting the importance of a Cpd I model system. A systematic benchmarking of thiolate-ligated Cpd I is performed using several generalized-gradient approximation (GGA) functionals in the Martins–Troullier and Vanderbilt ultrasoft pseudopotential schemes.

Automated Force Field Parameterization for Nonpolarizable and Polarizable Atomic Models Based on Ab Initio Target Data

Lei Huang and Benoît Roux [Argonne National Laboratory,]

J. Chem. Theor. and Comp, **9**, 3543–3556, 2013.

A!

Classical molecular dynamics (MD) simulations based on atomistic models are increasingly used to study a wide range of biological systems. A prerequisite for meaningful results from such simulations is an accurate molecular mechanical force field. Most biomolecular simulations are currently based on the widely used AMBER and CHARMM force fields, which were parametrized and optimized to cover a small set of basic compounds corresponding to the natural amino acids and nucleic acid bases. Atomic models of additional compounds are commonly generated by analogy to the parameter set of a given force field.

Simple Method for Simulating the Mixture of Atomistic and Coarse-Grained Molecular Systems

Pandian Sokkar, Sun Mi Choi, and Young Min Rhee [Pohang University of Science and Technology (POSTECH),]

J. Chem. Theor. and Comp, **9**, 3728–3739, 2013.

The existing methods for combining these two resolutions tend to require heavy parametrizations or sometimes lack in transferability to other systems of interest, and further developments toward such directions are highly required. We report here a simple protocol to combine CG and FG systems in a single simulation, using the standard FG and CG force field models by adopting a series of small proteins as test cases. Our method makes use of virtual sites as reported earlier for relatively simple butane and dialaine systems, to bridge the interaction between FG protein atoms and CG water.

Potentials and Parameters (Cont'd)

The First Three Coefficients in the High Temperature Series Expansion of Free Energy for Simple Potential Models with Hard-Sphere Cores and Continuous Tails

Shiqi Zhou [Central South University] , J. R. Solana

J. Phys. Chem. B., **117**, 9305–9313, 2013**.**

The first three coefficients of the high temperature series expansion (HTSE) of the Helmholtz free energy for a number of simple potential models with hard-sphere cores plus continuous tails are obtained for the first time from Monte Carlo simulations. The potential models considered include Square-well, Sutherland, attractive Yukawa, and triangle-well with different potential ranges, as well as a model potential qualitatively resembling the depletion potential in colloidal dispersions.

Free Energy Perturbation

Free Energy of Solvated Salt Bridges: A Simulation and Experimental Study

Andrew D. White, Andrew J. Keefe, Jean-Rene Ella-Menye, Ann K. Nowinski, Qing Shao, Jim Pfaendtner, and Shaoyi Jiang [University of Washington,]

J. Phys. Chem. B., **117**, 7254–7259, 2013**.**

Using well-tempered metadynamics, we have calculated salt bridge free energy surfaces in water and confirmed the results with NMR experiments. The simulations give binding free energies, quantitative ranking of salt bridging strength, and insights into the hydration of the salt bridges. The arginine–aspartate salt bridge was found to be the weakest and arginine-glutamate the strongest, showing that arginine can discriminate between aspartate and glutamate, whereas the salt bridges with lysine are indistinguishable in their free energy.

QM and QM/MM

Adenosine Triphosphate Hydrolysis Mechanism in Kinesin Studied by Combined Quantum-Mechanical/Molecular-Mechanical Metadynamics Simulations

Matthew J. McGrath , I.-F. Will Kuo, Shigehiko Hayashi, and Shoji Takada [Kyoto University]

J. Am. Chem. Soc., 2013, **135**, 8908–8919

Kinesin is a molecular motor that hydrolyzes adenosine triphosphate (ATP) and moves along microtubules against load. While motility and atomic structures have been well-characterized for various members of the kinesin family, not much is known about ATP hydrolysis inside the active site. Here, we study ATP hydrolysis mechanisms in the kinesin-5 protein Eg5 by using combined quantum mechanics/molecular mechanics metadynamics simulations.

Stabilization of Different Types of Transition States in a Single Enzyme Active Site: QM/MM Analysis of Enzymes in the Alkaline Phosphatase Superfamily

Guanhua Hou and Qiang Cui [University of Wisconsin-Madison]

J. Am. Chem. Soc., 2013, **135**, 10457–10469

The first step for the hydrolysis of a phosphate monoester (pNPP2–) in enzymes of the alkaline phosphatase (AP) superfamily, R166S AP and wild-type NPP, is studied using QM/MM simulations based on an approximate density functional theory (SCC-DFTBPR) and a recently introduced QM/MM interaction Hamiltonian. The calculations suggest that similar loose transition states are involved in both enzymes, despite the fact that phosphate monoesters are the cognate substrates for AP but promiscuous substrates for NPP.

QM and QM/MM (Cont'd)

Fast and accurate generation of ab initio quality atomic charges using nonparametric statistical regression

Brajesh K. Rai [Pfizer Worldwide Research and Development], Gregory A. Bakken

J. Comp. Chem., **34**, 1661–1671, 2013.

S!

We introduce a class of partial atomic charge assignment method that provides ab initio quality description of the electrostatics of bioorganic molecules. The method uses a set of models that neither have a fixed functional form nor require a fixed set of parameters, and therefore are capable of capturing the complexities of the charge distribution in great detail. Random Forest regression is used to build separate charge models for elements H, C, N, O, F, S, and Cl, using training data consisting of partial charges along with a description of their surrounding chemical environments.

Polarized Protein-Specific Charges from Atoms-in-Molecule Electron Density Partitioning

Louis P. Lee, Daniel J. Cole [Cavendish Laboratory], Chris-Kriton Skylaris, William L. Jorgensen, and Mike C. Payne

J. Chem. Theor. and Comp, **9**, 2981–2991, 2013.

Atomic partial charges for use in traditional force fields for biomolecular simulation are often fit to the electrostatic potentials of small molecules and, hence, neglect large-scale electronic polarization. We implement the density derived electrostatic and chemical charges method in the linear-scaling density functional theory code ONETEP. Our implementation allows the straightforward derivation of partial atomic charges for systems comprising thousands of atoms, including entire proteins. We demonstrate that the derived charges are chemically intuitive, reproduce ab initioelectrostatic potentials of proteins and are transferable between closely related systems.

Efficient Methods for the Quantum Chemical Treatment of Protein Structures: The Effects of London-Dispersion and Basis-Set Incompleteness on Peptide and Water-Cluster Geometries

Lars Goerigk and Jeffrey R. Reimers [The University of Sydney,]

J. Chem. Theor. and Comp, **9**, 3240–3251, 2013.

We demonstrate how quantum chemical Hartree–Fock (HF) or density functional theory (DFT) optimizations with small basis sets of peptide and water cluster structures are decisively improved if London-dispersion effects, the basis-set-superposition error (BSSE), and other basis-set incompleteness errors are addressed. We concentrate on three empirical corrections to these problems advanced by Grimme and co-workers that lead to computational strategies that are both accurate and efficient. Our analysis encompasses a reoptimized version of Hobza's P26 set of tripeptide structures, a new test set of conformers of cysteine dimers, and isomers of the water hexamer.

Acceleration of Semiempirical Quantum Mechanical Calculations by Extended Lagrangian Molecular Dynamics Approach

Kwangho Nam [Umeå University]

J. Chem. Theor. and Comp, **9**, 3393–3403, 2013.

The implementation and performance of the atom-centered density matrix propagation (ADMP) [J. Chem. Phys. 2001, 114, 9758] and the curvy-steps (CURV) methods [J. Chem. Phys. 2004, 121, 1152] are described. These methods solve the electronic Schrödinger equation approximately by propagating the electronic degrees of freedom using the extended Lagrangian molecular dynamics (ELMD) simulation approach. The ADMP and CURV methods are implemented and parallelized to accelerate semiempirical quantum mechanical (QM) methods (such as the MNDO, AM1, PM3, MNDO/d, and AM1/d methods).

QM and QM/MM (Cont'd)

Convergence of QM/MM and Cluster Models for the Spectroscopic Properties of the Oxygen-Evolving Complex in Photosystem II

Marius Retegan, Frank Neese, and Dimitrios A. Pantazis [Max Planck Institute for Chemical Energy Conversion,]

J. Chem. Theor. and Comp, **9**, 3832–3842, 2013.

The latest crystal structure of photosystem II at 1.9 Å resolution, which resolves the topology of the Mn4CaO5 oxygen evolving complex (OEC) at atomistic detail, enables a better correlation between structural features and spectroscopic properties than ever before. Building on the refined crystallographic model of the OEC and the protein, we present combined QM/MM studies of the spectroscopic properties of the natural catalyst embedded in the protein matrix. Focusing on the S2 state of the catalytic cycle, we examine the convergence of not only structural parameters but also of the intracluster magnetic interactions in terms of exchange coupling constants and of experimentally relevant 55Mn, 17O, and 14N hyperfine coupling constants with respect to QM/MM partitioning using five QM regions of increasing size.

Unusual Emitting States of the Kindling Fluorescent Protein: Appearance of the Cationic Chromophore in the GFP Family

Bella L. Grigorenko [M.V. Lomonosov Moscow State University,], Igor V. Polyakov, Alexander P. Savitsky, and Alexander V. Nemukhin

J. Phys. Chem. B., **117**, 7228–7234, 2013**.**

The kindling fluorescent protein (KFP), the Ala143Gly variant of the natural chromoprotein asFP595, is a prospective biomarker in live cells. Following the results of QM/MM calculations, we predict that excitation of the protein under certain conditions, favoring formation of KFP fractions with the neutral chromophore, should result in fluorescence from the cationic form of the chromophore which is unusual for the members of the green fluorescent protein family.

Quantum Mechanical Calculations of Xanthophyll–Chlorophyll Electronic Coupling in the Light-Harvesting Antenna of Photosystem II of Higher Plants

C. D. P. Duffy [University of London,], L. Valkunas, and A. V. Ruban

J. Phys. Chem. B., **117**, 7605–7614, 2013**.**

Light-harvesting by the xanthophylls in the antenna of photosystem II (PSII) is a very efficient process (with 80% of the absorbed energy being transfer to chlorophyll). However, the efficiencies of the individual xanthophylls vary considerably, with violaxanthin in LHCII contributing very little to light-harvesting. To investigate the origin of the variation we used Time Dependent Density Functional Theory to model the Coulombic interactions between the xanthophyll 11Bu+ states and the chlorophyll Soret band states in the LHCII and CP29 antenna complexes.

Efficient Parallel Implementations of QM/MM-REMD (Quantum Mechanical/Molecular Mechanics-Replica-Exchange MD) and Umbrella Sampling: Isomerization of H2O2 in Aqueous Solution

Dmitri G. Fedorov , Yuji Sugita , and Cheol Ho Choi [Kyungpook National University,]

J. Phys. Chem. B., **117**, 7996–8002, 2013**.**

An efficient parallel implementation of QM/MM-based replica-exchange molecular dynamics (REMD) as well as umbrella samplings techniques was proposed by adopting the generalized distributed data interface (GDDI). Parallelization speed-up of 40.5 on 48 cores was achieved, making our QM/MM-MD engine a robust tool for studying complex chemical dynamics in solution. They were comparatively used to study the torsional isomerization of hydrogen peroxide in aqueous solution.

QM and QM/MM (Cont'd)

Computational Study of the Structure and Electronic Circular Dichroism Spectroscopy of Blue Copper Proteins

Hainam Do, Robert J. Deeth, and Nicholas A. Besley [University of Nottingham, University Park,

J. Phys. Chem. B., **117**, 8105–8112, 2013**.**

The calculation of the electronic circular dichroism (CD) spectra of the oxidized form of the blue copper proteins plastocyanin and cucumber basic protein and the relationship between the observed spectral features and the structure of the active site of the protein is investigated. Excitation energies and transition strengths are computed using multireference configuration interaction, and it is shown that computed spectra based on coordinates from the crystal structure or a single structure optimized in quantum mechanics/molecular mechanics (QM/MM) or ligand field molecular mechanics (LFMM) are qualitatively incorrect.

Can Arsenates Replace Phosphates in Natural Biochemical Processes? A Computational Study

A. K. Jissy and Ayan Datta [Indian Association for the Cultivation of Science,]

J. Phys. Chem. B., **117**, 8340–8346, 2013**.**

A bacterial strain, GFAJ-1 was recently proposed to be substituting arsenic for phosphorus to sustain its growth. We have performed theoretical calculations for analyzing this controversial hypothesis by examining the addition of phosphate to ribose and glucose. Dispersion corrected Density Functional Theory (DFT) calculations in small molecules and QM/MM calculations on clusters derived from crystal structure are performed on structures involved in phosphorylation, considering both phosphates and arsenates. The exothermicity as well as the activation barriers for phosphate and arsenate transfer were examined.

On the Nature of the Hydrogen Bonds to Neutral Ubiquinone in the QA Binding Site in Purple Bacterial Photosynthetic Reaction Centers

Nan Zhao and Gary Hastings [Georgia State University,]

J. Phys. Chem. B., **117**, 8705-8713, 2013**.**

The nature of hydrogen bonding to pigments in protein complexes is currently a topic of some debate. The debate centers on whether hydrogen bonds can be understood on purely electrostatic grounds or whether they need to be considered quantum mechanically. This distinction is of current relevance primarily because of the application of QM/MM computational methods to the study of biological problems. To address this problem we have used QM/MM methods to study the neutral state of the hydrogen bonded ubiquinone molecule termed QA that functions as an electron transfer cofactor in purple bacterial photosynthetic reaction centers.

Comparative or Homology Modeling

Structure prediction and molecular dynamics simulations of a G-protein coupled receptor: human CCR2 receptor

Rajesh Singh & M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Biomol. Stru. and Dyn., ***31***, 694-715, *2013.*

CC chemokine receptor type-2 (CCR2) is a member of G-protein coupled receptors superfamily, expressed on the cell surface of monocytes and macrophages. It binds to the monocyte chemoattractant protein-1, a CC chemokine, produced at the sites of inflammation and infection. A homology model of human CCR2 receptor based on the recently available C-X-C chemokine recepor-4 crystal structure has been reported. Ligand information was used as an essential element in the homology modeling process. Six known CCR2 antagonists were docked into the model using simple and induced fit docking procedure.

Structural and functional insights on folate receptor α (FRα) by homology modeling, ligand docking and molecular dynamics

Stefano Della-Longa [Università dell'Aquila], Alessandro Arcovito

J. Mol.Graph. and Mod., **44,** 197–207, 2013

Folate receptor α (FRα) is a cell surface, glycophosphatidylinositol (GPI)-anchored protein with a high affinity for its ligand partner, which is highly expressed in malignant cells and has been selected as a therapeutic target and marker for the diagnosis of cancer. Three-dimensional models of the FRα structure have been derived with the recent homology modeling packages, using the crystal structure of the riboflavin-binding protein (RfBP) as a template.

Description of local and global shape properties of protein helices

Zhanyong Guo, Elfi Kraka, Dieter Cremer[Southern Methodist University,]

J. Mol.Mod., **19,** 2901-2911, 2013.

A new method, dubbed "HAXIS" is introduced to describe local and global shape properties of a protein helix via its axis. HAXIS is based on coarse-graining and spline-fitting of the helix backbone. At each Cα anchor point of the backbone, a Frenet frame is calculated, which directly provides the local vector presentation of the helix. After cubic spline-fitting of the axis line, its curvature and torsion are calculated.

Interactions between Voltage Sensor and Pore Domains in a hERG K+Channel Model from Molecular Simulations and the Effects of a Voltage Sensor Mutation

Charlotte K. Colenso , Richard B. Sessions , Yi H. Zhang , Jules C. Hancox , and Christopher E. Dempsey

J.Chem. Infor. and Mod. **53**, 1358–1370, 2013.

The hERG K+ channel is important for establishing normal electrical activity in the human heart. The channel's unique gating response to membrane potential changes indicates specific interactions between voltage sensor and pore domains that are poorly understood. In the absence of a crystal structure we constructed a homology model of the full hERG membrane domain and performed 0.5 μs molecular dynamics (MD) simulations in a hydrated membrane. The simulations identify potential interactions involving residues at the extracellular surface of S1 in the voltage sensor and at the N-terminal end of the pore helix in the hERG model.

Comparative and Homology Modeling (Cont'd)

Iterative Molecular Dynamics—Rosetta Protein Structure Refinement Protocol to Improve Model Quality

Steffen Lindert [University of California San Diego], Jens Meiler, and J. Andrew McCammon
J. Chem. Theor. and Comp, **9**, 3843–3847, 2013.

We test the hypothesis that iteration of Rosetta with an orthogonal sampling and scoring strategy might facilitate exploration of conformational space. Specifically, we run short molecular dynamics (MD) simulations on models created by de novo folding of large proteins into cryoEM density maps to enable sampling of conformational space not directly accessible to Rosetta and thus provide an escape route from the conformational traps. We present a combined MD–Rosetta protein structure refinement protocol that can overcome some of these sampling limitations.

Ligand Docking

Modulation of In-Membrane Receptor Clustering upon Binding of Multivalent Ligands

Anna Grochmal, Elena Ferrero, Lilia Milanesi, and Salvador Tomas [Birkbeck University of London,]

J. Am. Chem. Soc., 2013, **135**, 10172–10177

In living cells and biomimetic systems alike, multivalent ligands in solution can induce clustering of membrane receptors. The link between the receptor clustering and the ligand binding remains, however, poorly defined. Using minimalist divalent ligands, we develop a model that allows quantifying the modulation of receptor clustering by binding of ligands with any number of binding sites.

Molecular dynamics simulations of isoleucine-release pathway in GAF domain of N-CodY from *Bacillus Subtilis*

Baoping Ling [Qufu Normal University], Min Sun, Siwei Bi, Zhihong Jing, Zhiguo Wang

J. Mol.Graph. and Mod., **44,** 232–240, 2013.

The GAF domain located in the N-terminal motifs of CodY (N-CodY) is responsible for increasing the affinity of CodY to its target sites on DNA by its interaction with the branched chain amino acids (BCAAs) involving isoleucine, leucine and valine. The study of the interaction of GAF domain with isoleucine gains much attention in recent years, but the mechanism of isoleucine release still remains unclear. In this paper, a conventional molecular dynamics (MD) and force probe molecular dynamics (FPMD) simulations have been performed with the aim to understand how the isoleucine ligand escapes from the GAF domain of N-CodY from *Bacillus subtilis*.

3D Matched Pairs: Integrating Ligand- and Structure-Based Knowledge for Ligand Design and Receptor Annotation

Shana L. Posy, Brian L. Claus, Matt E. Pokross, and Stephen R. Johnson [Bristol-Myers Squibb Research and Development]

J.Chem. Infor. and Mod. **53**, 1576–1588, 2013.

We describe an extension to the matched molecular pairs approach that merges pairwise activity differences with three-dimensional contextual information derived from X-ray crystal structures and binding pose predictions. The incorporation of 3D binding poses allows the direct comparison of structural changes to diverse chemotypes in particular binding pockets, facilitating the transfer of SAR from one series to another.

Ligand Docking (Cont'd)

Water Network Perturbation in Ligand Binding: Adenosine A2A Antagonists as a Case Study

Andrea Bortolato [Heptares Therapeutics Ltd, BioPark,], Ben G. Tehan, Michael S. Bodnarchuk, Jonathan W. Essex, and Jonathan S. Mason

J.Chem. Infor. and Mod. **53**, 1700–1713, 2013

S!

Recent efforts in the computational evaluation of the thermodynamic properties of water molecules have resulted in the development of promising new in silico methods to evaluate the role of water in ligand binding. These methods include WaterMap, SZMAP, GRID/CRY probe, and Grand Canonical Monte Carlo simulations. We have for the first time extended these approaches toward the prediction of kinetics for small molecules and of relative free energy of binding with a focus on the perturbation of the water network and application to large diverse data sets.

Assessing the Performance of MM/PBSA and MM/GBSA Methods. 3. The Impact of Force Fields and Ligand Charge Models

Lei Xu, Huiyong Sun, Youyong Li, Junmei Wang, and Tingjun Hou [Zhejiang University,]

J. Phys. Chem. B., **117**, 8408–8421, 2013**.**

Here, we systematically investigated how the force fields and the partial charge models for ligands affect the ranking performance of the binding free energies predicted by the Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) approaches.

Computational insights into the binding modes of Sr-Rex with cofactor NADH/NAD$^+$and operator DNA

Yanyan Chu, Weihua Li, Jianfeng Wang, Guixia Liu, Yun Tang [East China University of Science and Technology]

J. Mol.Mod., **19,** 3143-3151, 2013.

The transcriptional repressor Rex plays key roles in modulating respiratory gene expression. It senses the redox poise of the NAD(H) pool. Rex from *Streptomyces rimosus* (Sr-Rex) is a newly identified protein. Its structure and complex with substrates are not determined yet. In this study, the three-dimensional (3D) structural models of Sr-Rex dimer and its complex with cofactors were constructed by homology modeling. The stability of the constructed Sr-Rex models and the detailed interactions between Sr-Rex and cofactors were further investigated by molecular dynamics simulations.

Design of Linear Ligands for Selective Separation Using a Genetic Algorithm Applied to Molecular Architecture

Erik E. Santiso, Nicholas Musolino, and Bernhardt L. Trout [Institute of Technology, Cambridge,]

J.Chem. Infor. and Mod. **53**, 1638–1660, 2013.

Continuous purification of chemical reaction products through adsorption-based operations during workup may present advantages over batch chromatography or crystallization. In pharmaceutical syntheses, however, the desired product is often structurally similar to byproducts or unconverted reactant, so that identifying a suitable adsorption medium is challenging. We developed an in silico screening process to design organic ligands which, when chemically bound to a solid surface, would constitute an effective adsorption for a pharmaceutically relevant mixture of reaction products.

Ligand Docking (Cont'd)

Improved Docking of Polypeptides with Glide

Ivan Tubert-Brohman , Woody Sherman , Matt Repasky, and Thijs Beuming

J.Chem. Infor. and Mod. **53**, 1689–1699, 2013.

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Predicting the binding mode of flexible polypeptides to proteins is an important task that falls outside the domain of applicability of most small molecule and protein–protein docking tools. Here, we test the small molecule flexible ligand docking program Glide on a set of 19 non-α-helical peptides and systematically improve pose prediction accuracy by enhancing Glide sampling for flexible polypeptides. In addition, scoring of the poses was improved by post-processing with physics-based implicit solvent MM-GBSA calculations.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 44, July 2013.

81–90 **Complex between *Human* RNase HI and the phosphonate-DNA/RNA duplex: Molecular dynamics study**Kamil Maláč , Ivan Barvík[Charles University,]

See Applications / Protein-Nucleic acids.

91–103 **Is the conformational flexibility of piperazine derivatives important to inhibit HIV-1 replication?** Cátia Teixeira [Univ Paris Diderot,], Nawal Serradji, Souad Amroune, Karen Storck, Christine Rogez-Kreuz, Pascal Clayette, Florent Barbault, François Maurel

See Applications / Protein Dynamics.

104–112 **AutoGrow 3.0: An improved algorithm for chemically tractable, semi-automated protein inhibitor design** Jacob D. Durrant [University of California San Diego], Steffen Lindert, J. Andrew McCammon

See Applications / Bioinformatics.

113–119 **Prediction of boiling points of organic compounds by QSPR tools** Yi-min Dai [Changsha University of Science and Technology,] ,Zhi-ping Zhu, Zhong Cao, Yue-fei Zhang, Ju-lan Zeng, Xun Li

The novel electro-negativity topological descriptors of Y_C, W_C were derived from molecular structure by equilibrium electro-negativity of atom and relative bond length of molecule. The quantitative structure–property relationships (QSPR) between descriptors of Y_C, W_C as well as path number parameter P_3 and the normal boiling points of 80 alkanes, 65 unsaturated hydrocarbons and 70 alcohols were obtained separately.

120–128 **Investigation of simple and water assisted tautomerism in a derivative of 1,3,4-oxadiazole: A DFT study** Behzad Chahkandi[Islamic Azad University], Sayyed Faramarz Tayyari, Maliheh Bakhshaei, Mohammad Chahkandi

Investigation of tautomerism and transition states in a derivative of 1,3,4-oxadiazole (A, B, C and D) in the gas phase and in solution and in a micro hydrated environment with 1–3 water molecules was performed by calculations at the DFT-B3LYP/6-311++G(*d*,*p*) level of theory.

129–135 **Hybrid density functional based study on the band structure of trioctahedral mica and its dependence on the variation of Fe^{2+}content ,**V. Timón [InstitutoAndaluz de Ciencias de la Tierra] , C.S. Praveen, E. Escamilla-Roa, M. Valant

A hybrid density functional based study of a phyllosilicate (PS) is presented here for the first time. Using all-electron electronic structure calculations with the B3LYP hybrid functional, we have investigated the electronic and structural properties of a series of trioctahedral 1M-polytype K-bearing micas starting from phlogopite (the Mg-end member), ending with the annite (the Fe-end member), and passing through the biotite (a solid solution of the end members).

136–144 **Study of the interaction of *Huperzia saururus* Lycopodium alkaloids with the acetylcholinesterase enzyme,** Marcelo Puiatti [Universidad Nacional de Córdoba] , José Luis Borioni, Mariana Guadalupe Vallejo, José Luis Cabrera, Alicia Mariel Agnese, María Gabriela Ortega, Adriana Beatríz Pierini

See Applications / Membrane Proteins.

145–154 **Interactions of acetylcholine binding site residues contributing to nicotinic acetylcholine receptor gating: Role of residues Y93, Y190, K145 and D200** Prema L. Mallipeddi, Steen E. Pedersen, James M. Briggs [University of Houston]

See Applications / Ligand Binding.

155–160 **Molecular modeling revealed that ligand dissociation from thyroid hormone receptors is affected by receptor heterodimerization** Shulin Zhuang[Zhejiang University], Lingling Bao, Apichart Linhananta, Weiping Liu

See Applications / Ligand Binding.

161–167 **Homology modeling study toward identifying structural properties in the HA2 B-loop that would influence the HA1 receptor-binding site** Marni E. Cueno, Kenichi Imai, Kazufumi Shimizu, Kuniyasu Ochiai [Nihon University School of Dentistry]

See Applications / Homology Modeling.

168–176 **Modeling of multifunctional donor-bridge-acceptor 4,6-di(thiophen-2-yl)pyrimidine derivatives: A first principles study** Ahmad Irfan [King Khalid University,], Abdullah G. Al-Sehemi, Mohammad Sultan Al-Assiri

We have modeled multifunctional compounds by pi-elongation and push–pull strategy from the 4,6-di(thiophen-2-yl)pyrimidine. The ground state geometries have been optimized by density functional theory while excited state geometries were optimized by time dependent density functional theory (TDDFT). Structure–property relationship, electronic, optical and charge transfer properties (ionization potential, electron affinity and reorganization energies) were computed and discussed.

177–187 **The emerging role of cloud computing in molecular modeling** Jean-Paul Ebejer, Simone Fulle, Garrett M. Morris, Paul W. Finn[Oxford Centre for Innovation,]

See Applications / Bioinformatics.

188–196 **Similarity-based virtual screening for microtubule stabilizers reveals novel antimitotic scaffold** Ahmed T. Ayoub, Mariusz Klobukowski, Jack Tuszynski[University of Alberta,]

Microtubules are among the most studied and best characterized cancer targets identified to date. Many microtubule stabilizers have been introduced so far that work by disrupting the dynamic instability of microtubules causing mitotic block and apoptosis. Here we employ a novel similarity-based virtual screening approach in the hope of finding other microtubule stabilizers that perform better and have lower toxicity and resistance.

197–207 **Structural and functional insights on folate receptor α (FRα) by homology modeling, ligand docking and molecular dynamics** Stefano Della-Longa [Università dell'Aquila], Alessandro Arcovito

See Methodology / Homology Modeling.

208–219 **Characterization and comparison of pore landscapes in crystalline porous materials** Marielle Pinheiro, Richard L. Martin, Chris H. Rycroft, Andrew Jones, Enrique Iglesia, Maciej Haranczyk [Lawrence Berkeley National Laboratory,]

Crystalline porous materials have many applications, including catalysis and separations. Identifying suitable materials for a given application can be achieved by screening material databases. Here, we discuss algorithms for the calculation of two types of pore landscape descriptors: pore size distributions and stochastic rays.

220–231 ***In silico* design: Extended molecular dynamic simulations of a new series of dually acting inhibitors against EGFR and HER2** Marawan Ahmed, Maiada M. Sadek, Khaled A. Abouzid, Feng Wang[Swinburne University of Technology]

See Applications / Ligand Binding.

232–240 **Molecular dynamics simulations of isoleucine-release pathway in GAF domain of N-CodY from *Bacillus Subtilis*** Baoping Ling [Qufu Normal University,], Min Sun, Siwei Bi, Zhihong Jing, Zhiguo Wang

See Applications / Ligand Binding.

241–252 **Structure based design towards the identification of novel binding sites and inhibitors for the chikungunya envelope virus** Adel A. Rashad, Paul A. Keller[University of Wollongong,]

Chikungunya virus is an emerging arbovirus that is widespread in tropical regions and is spreading quickly to temperate climates with recent epidemics in Africa, Asia, Europe and the Americas. We describe here for the first time the identification of novel sites for potential binding on the chikungunya glycoprotein complexes and the identification of possible antagonists for these sites through virtual screening using two successive docking scores.

253–265 **Crystal structure, stability and spectroscopic properties of methane and CO_2 hydrates** Ruben Martos-Villa, Misaela Francisco-Márquez, M. Pilar Mata, C. Ignacio Sainz-Díaz[CSIC-Universidad de Granada,]

Methane hydrates are highly present in sea-floors and in other planets and their moons. The knowledge of stability and physical–chemical properties of methane hydrate crystal structure is important for evaluating some new green becoming technologies such as, strategies to produce natural gas from marine methane

hydrates and simultaneously store CO_2 as hydrates. Molecular Dynamic simulations have been also performed exploring different configurations reproducing the experimental crystallographic properties.

266–277 **Structural requirements of 3-carboxyl-4(1H)-quinolones as potential antimalarials from 2D and 3D QSAR analysis** Jiazhong Li [Lanzhou University], Shuyan Li, Chongliang Bai, Huanxiang Liu, Paola Gramatica

See Applications / Quantitative Structure-Activity Relations

Journal of Computational Chemistry, 34 (19), July 2013.

1611–1619 **Theoretical characterization and design of small molecule donor material containing naphthodithiophene central unit for efficient organic solar cells** Yu-Ai Duan, Yun Geng, Hai-Bin Li, Jun-Ling Jin, Yong Wu, Zhong-Min Su [Northeast Normal University]

To seek for high-performance small molecule donor materials used in heterojunction solar cell, six acceptor–donor–acceptor small molecules based on naphtho[2,3-b:6,7-b′]dithiophene (NDT) units with different acceptor units were designed and characterized using density functional theory and time-dependent density functional theory.

1620–1635 **A simple but effective modeling strategy for structural properties of non-heme Fe(II) sites in proteins: Test of force field models and application to proteins in the AlkB family** Xueqin Pang, Keli Han, Qiang Cui [University of Wisconsin]

See Methodology / Potentilas and Parameters.

1636–1646 **Nonfitting protein–ligand interaction scoring function based on first-principles theoretical chemistry methods: Development and application on kinase inhibitors** Li Rao, Igor Ying Zhang, Wenping Guo, Li Feng, Eric Meggers, Xin Xu [Philipps-University Marburg]

See Applications / Membrane Proteins.

1647–1660 **Cytochrome P450 compound I in the plane wave pseudopotential framework: GGA electronic and geometric structure of thiolate-ligated iron(IV)–oxo porphyrin** Justin E. Elenewski, John C Hackett [Virginia Commonwealth University]

See Methodology / Potentilas and Parameters.

1661–1671 **Fast and accurate generation of ab initio quality atomic charges using nonparametric statistical regression** Brajesh K. Rai [Pfizer Worldwide Research and Development], Gregory A. Bakken

See Methodology / QM and QM/MM.

1686–1696 **Accurate double many-body expansion potential energy surface by extrapolation to the complete basis set limit and dynamics calculations for ground state of NH2** Yongqing Li, Jiuchuang Yuan, Maodu Chen [Dalian University of Technology, Dalian,], Fengcai Ma, Mengtao Sun

An accurate single-sheeted double many-body expansion potential energy surface is reported for the title system. A switching function formalism has been used to warrant the correct behavior at the and dissociation channels involving nitrogen in the ground and first excited states.

1697–1705 **PHAISTOS: A framework for Markov chain Monte Carlo simulation and inference of protein structure** Wouter Boomsma [University of Copenhagen], Jes Frellsen, Tim Harder, Sandro Bottaro, Kristoffer E. Johansson, Pengfei Tian, Kasper Stovgaard, Christian Andreetta, Simon Olsson, Jan B. Valentin, Lubomir D. Antonov, Anders S. Christensen, Mikael Borg, Jan H. Jensen, Kresten Lindorff-Larsen, Jesper Ferkinghoff-Borg,homas Hamelryck

See Applications / Bioinformatics.

Journal of Computational Chemistry, 34 (20), July 2013.

1707–1718 **IMSPeptider: A computational peptide collision cross-section area calculator based on a novel molecular dynamics simulation protocol** Ranieri V. de Carvalho, Daniel Lopez-Ferrer, Katia S. Guimarães, Roberto D. Lins[Federal University of Pernambuco]

See Applications / Protein Dynamics.

1719–1734 **Multiobjective evolutionary algorithm with many tables for purely ab initio protein structure prediction** Christiane Regina Soares Brasil[University of São Paulo],Alexandre Claudio Botazzo Delbem,Fernando Luís Barroso da Silva

See Applications / Protein Structure prediction.

1735–1742 **Quantum wave packet and quasiclassical trajectory studies of the reaction H(2S) + CH(X2Π; v = 0, j = 1) → C(1D) + H2(X1 Σg+): Coriolis coupling effects and stereodynamics** Ruifeng Lu [Nanjing University of Science and Technology], Yunhui Wang, Kaiming Deng

The quantum mechanics (QM) and quasiclassical trajectory (QCT) calculations have been carried out for the title reaction with the ground minimal allowed rotational state of CH (j = 1) on the 1 1A′ potential energy surface.

1743–1758 **DOT2: Macromolecular docking with improved biophysical models** Victoria A. Roberts[University of California] , Elaine E. Thompson, Michael E. Pique, Martin S. Perez, L. F. Ten Eyck

See Applications / Bioinformatics.

1759–1774 **Analytic derivatives for the XYG3 type of doubly hybrid density functionals: Theory, implementation, and assessment** Neil Qiang Su, Igor Ying Zhang, Xin Xu[Fudan University]

We present a theoretical development of the equations required to perform an analytic geometry optimization of a molecular system using the XYG3 type of doubly hybrid (xDH) functionals.

1775–1784 **Performance of density functional theory in computing nonresonant vibrational (hyper)polarizabilities** Ireneusz W. Bulik, Robert Zaleśny [Wroclaw University of Technology], Wojciech Bartkowiak, Josep M. Luis,Bernard Kirtman, Gustavo E. Scuseria, Aggelos Avramopoulos, Heribert Reis,Manthos G. Papadopoulos

A set of exchange-correlation functionals, including BLYP, PBE0, B3LYP, BHandHLYP, CAM-B3LYP, LC-BLYP, and HSE, has been used to determine static and dynamic nonresonant (nuclear relaxation) vibrational (hyper)polarizabilities for a series of all-trans polymethineimine (PMI) oligomers containing up to eight monomer units.

1785–1793 **Application of replica exchange umbrella sampling to protein structure refinement of nontemplate models** Mark A. Olson[USAMRIID, Fredrick], Michael S. Lee

See Applications / Protein Confirmational Analysis.

Journal of Computational Chemistry, 34 (21), July 2013.

1797–1799 **Low cost prediction of relative stabilities of hydrogen bonded complexes from atomic multipole moments for overly short intermolecular distances** Wiktor Beker, Karol M. Langner, Edyta Dyguda-Kazimierowicz, Mikołaj Feliks, W. Andrzej Sokalski [Wrocław University of Technology]

The relative stability of biologically relevant, hydrogen bonded complexes with shortened distances can be assessed at low cost by the electrostatic multipole term alone more successfully than by ab initio methods.

1800–1809 **Improved partition–expansion of two-center distributions involving slater functions** Rafael López[Universidad Autónoma de Madrid], Guillermo Ramírez, Ignacio Ema, Jaime Fernández Rico

The calculation of the electronic structure of large systems is facilitated by the substitution of the two-center distributions by their projections on auxiliary basis sets of one-center functions. An alternative is the partition–expansion method in which one first decides what part of the distribution is assigned to each center, and next expands each part in spherical harmonics times radial factors. The method is exact, requires neither auxiliary basis sets nor projections, and can be applied to Gaussian and Slater basis sets.

1810–1818 **PathOpt—A global transition state search approach: Outline of algorithm** Christoph Grebner, Lukas P. Pason,Bernd Engels[Julius-Maximilians-Universität Würzburg]

We propose a new algorithm to determine reaction paths and test its capability for Ar12 and Ar13 clusters. Its main ingredient is a search for the local minima on a (n−1) dimensional hyperplane (n = dimension of the complete system in Cartesian coordinates) lying perpendicular to the straight line connection between initial and final states.

within the T cell. In this study, we introduce a new methodology based on differential geometric parameters to describe MH deformations in a detailed and comparable way.

Journal of Computational Chemistry, 34 (22), August 2013.

1881–1889 **High–quality protein backbone reconstruction from alpha carbons using gaussian mixture models** Benjamin L. Moore, Lawrence A. Kelley,James Barber, James W. Murray, James T. MacDonald[South Kensington Campus, London,]

See Applications / Protein Structure prediction.

1890–1898 **^{129}Xe NMR chemical shift in Xe@C_{60} calculated at experimental conditions: Essential role of the relativity, dynamics, and explicit solvent** Stanislav Standara, Petr Kulhánek,Radek Marek, Michal Straka [Masaryk University,]

The isotropic ^{129}Xe nuclear magnetic resonance (NMR) chemical shift (CS) in Xe@C_{60} dissolved in liquid benzene was calculated by piecewise approximation to faithfully simulate the experimental conditions and to evaluate the role of different physical factors influencing the ^{129}Xe NMR CS.

1899–1906 **Influence of variation of a side chain on the folding equilibrium of a β-peptide: Limitations of one-step perturbation** Zhixiong Lin, Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

In a recent study (Lin et al., Helv. Chim. Acta 2011, **94**, 597), the one-step perturbation method was applied to tackle a challenging computational problem, that is, the calculation of the folding free enthalpies $\Delta G_{F,U}$ of six hepta-β-peptides with different, Ala, Val, Leu, Ile, Ser, or Thr, side chains in the fifth residue. Here, alternative reference-state Hamiltonians that better cover the conformational space relevant to these peptides are investigated, and post simulation rotational sampling of the χ_1 and χ_2 torsional angles of the fifth residue is carried out to sample different orientations of the side chain.

1907–1916 **Binding affinity of substituted ureido-benzenesulfonamide ligands to the carbonic anhydrase receptor: A theoretical study of enzyme inhibition** Chandan Sahu, Kaushik Sen, Srimanta Pakhira, Bhaskar Mondal, Abhijit K. Das [Indian Association for the Cultivation of Science, Jadavpur]

See Applications / Ligand Binding.

1917–1924 **Activation of C–H bond in methane by Pd atom from the bonding evolution theory perspective** Anton S. Nizovtsev [Siberian Branch of the Russian Academy of Sciences, Novosibirsk]

We report detailed study focused on the electron density redistribution during the simple oxidative addition reaction being the crucial stage of various catalytic processes.

1925–1936 **A homology/*ab initio* hybrid algorithm for sampling near-native protein conformations** Priyanka Dhingra, Bhyravabhotla Jayaram[Indian Institute of Technology, Hauz Khas, New Delhi,]

See Applications / Protein Structure prediction.

1937–1948 **Parallelization of a multiconfigurational perturbation theory** Steven Vancoillie [University of Leuven, Belgium], Mickaël G. Delcey,Roland Lindh, Victor Vysotskiy, Per-Åke Malmqvist, Valera Veryazov

n this work, we present a parallel approach to complete and restricted active space second-order perturbation theory, (CASPT2/RASPT2). We also make an assessment of the performance characteristics of its particular implementation in the Molcas quantum chemistry programming package. Parallel scaling is limited by memory and I/O bandwidth instead of available cores.

1949–1960 **Continuous development of schemes for parallel computing of the electrostatics in biological systems: Implementation in DelPhi** Chuan Li, Marharyta Petukh, Lin Li, Emil Alexov [Clemson University]

Due to the enormous importance of electrostatics in molecular biology, calculating the electrostatic potential and corresponding energies has become a standard computational approach for the study of biomolecules and nano-objects immersed in water and salt phase or other media. Here, we report further development of the parallelization scheme reported in our previous work (Li, et al., J. Comput. Chem. 2012, 33, 1960) to include parallelization of the molecular surface and energy calculations components of the algorithm.

1961-1967 **SIMPRE: A software package to calculate crystal field parameters, energy levels, and magnetic properties on mononuclear lanthanoid complexes based on charge distributions** José J. Baldoví, Salvador Cardona-Serra, Juan M. Clemente-Juan, Eugenio Coronado[Universidad de Valencia], Alejandro Gaita-Ariño,Andrew Palii

This work presents a fortran77 code based on an effective electrostatic model of point charges around a rare earth ion. The program calculates the full set of crystal field parameters, energy levels spectrum, and wave functions, as well as the magnetic properties such as the magnetization, the temperature dependence of the magnetic susceptibility, and the Schottky contribution to the specific heat.

1969–1974 **A morphometric approach for the accurate solvation thermodynamics of proteins and ligands** Yuichi Harano [Osaka University], Roland Roth, Shuntaro Chiba

We have developed a versatile method for calculating solvation thermodynamic quantities for molecules, starting from their atomic coordinates. The contribution of each atom to the thermodynamic quantities is estimated as a linear combination of four fundamental geometric measures of the atomic species, which are defined by Hadwiger's theorem, and the coefficients reflecting their solvation properties.

1975–1981 **The performance of density functional and wavefunction-based methods for 2D and 3D structures of Au_{10}** Daniel A. Götz [Technische Universität Darmstadt,, Rolf Schäfe, Peter Schwerdtfeger

The transition from 2D to 3D structures in small gold clusters occurs around 10 atoms. Density functional theory predicts a planar D_{2h}structure for Au_{10} in contrast to recent second-order Møller–Plesset perturbation theory calculations, which predict a 3D C_{2v} arrangement.

1982–1996 **First principle and ReaxFF molecular dynamics investigations of formaldehyde dissociation on Fe(100) surface** Takahiro Yamada [University of Dayton Research Institute], Donald K. Phelps,Adri C. T. van Duin

The study includes formaldehyde, formyl radical (HCO), and CO adsorption and dissociation energy calculations on the surface, adsorbate vibrational frequency calculations, density of states analysis of clean and adsorbed surfaces, complete potential energy diagram construction from formaldehyde to atomic carbon (C), hydrogen (H), and oxygen (O), simulation of formaldehyde adsorption and dissociation reaction on the surface using reactive force field, ReaxFF MD, and reaction rate calculations of adsorbates using transition state theory (TST).

1997–2005 **The α-effect exhibited in gas-phase S_N2@N and S_N2@C reactions** Yi Ren [Sichuan University], Xi-Guang We, Si-Jia Ren,Kai-Chung Lau, Ning-Bew Wong, Wai-Kee Li

In order to explore the existence of α-effect in gas-phase S_N2@N reactions, and to compare its similarity and difference with its counterpart in S_N2@C reactions, we have carried out a theoretical study on the reactivity of six α-oxy-Nus (FO^-, ClO^-, BrO^-, HOO^-, HSO^-, H_2NO^-) in the S_N2 reactions toward NR_2Cl (R = H, Me) and RCl (R = Me, *i*-Pr) using the $G2(+)_M$ theory.

2006–2013 **The ORP basis set designed for optical rotation calculations** Angelika Baranowska-Łączkowska [Kazimierz Wielki University] ,Krzysztof Z. Łączkowski

Details of generation of the optical rotation prediction (ORP) basis set developed for accurate optical rotation (OR) calculations are presented.

2014–2019 **Polarization functions for the modified m6-31G basis sets for atoms Ga through Kr** Alexander V. Mitin[Moscow State University]

The performances of the m6-31G, m6-31G(d,p), and m6-31G(2df,p) basis sets were examined in molecular calculations carried out by the density functional theory (DFT) method with B3LYP hybrid functional, Møller-Plesset perturbation theory of the second order (MP2), quadratic configuration interaction method with single and double substitutions and were compared with those for the known 6-31G basis sets as well as with the other similar 641 and 6-311G basis sets with and without polarization functions.

2020–2031 **A high-accuracy theoretical study of the CH_nP Systems $n = 1–3$** Ringo Rey-Villaverde, Hubert Cybulski, Jesús R. Flores [Universidad de Vigo], Berta Fernández

We have performed high-level electronic structure computations on the most important species of the CH_nP systems $n = 1–3$ to characterize them and provide reliable information about the equilibrium and vibrationally averaged molecular structures, rotational constants, vibrational frequencies (harmonic and anharmonic), formation enthalpies, and vertical excitation energies.

2032–2040 **A polarizable ellipsoidal force field for halogen bonds** Likai Du, Jun Gao [Shandong University], Fuzhen Bi, Lili Wang, Chengbu Liu

The anisotropic effects and short-range quantum effects are essential characters in the formation of halogen bonds. Since there are an array of applications of halogen bonds and much difficulty in modeling them in classical force fields, the current research reports solely the polarizable ellipsoidal force field (PEff) for halogen bonds.

2041–2054 **CENCALC: A computational tool for conformational entropy calculations from molecular simulations** Ernesto Suárez, Natalia Díaz,Jefferson Méndez, Dimas Suárez[Universidad de Oviedo]

We present the CENCALC software that has been designed to estimate the conformational entropy of single molecules from extended Molecular Dynamics (MD) simulations in the gas-phase or in solution. CENCALC uses both trajectory coordinates and topology information in order to characterize the conformational states of the molecule of interest by discretizing the time evolution of internal rotations.

Journal of Molecular Modeling, 19 (7), july 2013.

2689-2697 **Fine structure in the transition region: reaction force analyses of water-assisted proton transfers** Diana Yepes, Jane S. Murray, Juan C. Santos, Alejandro Toro-Labbé, Peter Politzer, Pablo Jaque[Universidad Andres Bello,]

We have analyzed the variation of the reaction force F(ξ) and the reaction force constant κ(ξ) along the intrinsic reaction coordinates ξ of the water-assisted proton transfer reactions of HX-N = Y (X,Y = O,S). The profile of the force constant of the vibration associated with the reactive mode, k ξ (ξ), was also determined.

2699-2714 **Half-metallicity of graphene nanoribbons and related systems: a new quantum mechanical El Dorado for nanotechnologies … or a hype for materials scientists?** Michael S. Deleuze [Hasselt University], Matija Huzak, Balázs Hajgató

In this work we discuss in some computational and analytical details the issue of half-metallicity in zig-zag graphene nanoribbons and nanoislands of finite width, i.e. the coexistence of metallic nature for electrons with one spin orientation and insulating nature for the electrons of opposite spin, which has been recently predicted from so-called first-principle calculations employing Density Functional Theory

2715-2722 **Explaining reaction mechanisms using the dual descriptor: a complementary tool to the molecular electrostatic potential** Jorge Ignacio Martínez-Araya[Universidad Pedro de Valdivia,]

The intrinsic reactivity of cyanide when interacting with a silver cation was rationalized using the dual descriptor (DD) as a complement to the molecular electrostatic potential (MEP) in order to predict interactions at the local level.

2723-2737 **Bis(heptalene) "submarine" metal dimer sandwich compounds (C12H10)2M2 (M = Ti, V, Cr, Mn, Fe, Co, Ni)** Huidong Li, Hao Feng [Xihua University], Weiguo Sun, Qunchao Fan, Yaoming Xie, R. Bruce King, Henry F. Schaefer III

The bis(heptalene)dimetal complexes (C12H10)2M2 of the first row transition metals from Ti to Ni are predicted by density functional theory to exhibit "submarine" sandwich structures with a pair of metal atoms sandwiched between the two heptalene rings.

2739-2746 **Trends in σ-hole strengths and interactions of F3MX molecules (M = C, Si, Ge and X = F, Cl, Br, I)**Ashwini Bundhun, Ponnadurai Ramasami [University of Mauritius,], Jane S. Murray, Peter Politzer

It is well-established that many covalently-bonded atoms of Groups IV–VII have directionally-specific regions of positive electrostatic potential (σ-holes) through which they can interact with negative sites. In the case of Group VII, this is called "halogen bonding." We have studied two series of molecules: the F3MX and, for comparison, the H3MX (M = C, Si and Ge; X = F, Cl, Br and I).

2747-2758 **ETS-NOCV description of σ-hole bonding** Karol Dyduch, Mariusz P. Mitoraj, Artur Michalak [Jagiellonian University]

The ETS-NOCV analysis was applied to describe the σ-hole in a systematic way in a series of halogen compounds, CF3-X (X = I, Br, Cl, F), CH3I, and C(CH3)nH3-n-I (n = 1,2,3), as well as for the example germanium-based systems. GeXH3, X = F, Cl, H. Further, the ETS-NOCV analysis was used to characterize bonding with ammonia for these systems.

2759-2766 **Modulating weak intramolecular interactions through the formation of beryllium bonds: complexes between squaric acid and BeH2**M. Merced Montero-Campillo, Al Mokhtar Lamsabhi, Otilia Mó, Manuel Yáñez [Universidad Autónoma de Madrid,]

The electronic structure of the two most stable isomers of squaric acid and their complexes with BeH2 were investigated at the B3LYP/6-311 + G(3df,2p)// B3LYP/6-31 + G(d,p) level of theory.

2767-2771 **The density per particle can be used as the fundamental descriptor for systems with rapidly decaying external potentials** Paul W. Ayers [McMaster University]

For systems of electrons bound by potentials that decay faster than 1/r asymptotically, the density per particle determines the number of electrons and therefore the electron density. The density per particle, commonly called the shape function, can thus be used as the fundamental descriptor of systems with rapidly decaying external potentials. This result is analogous to a result that is known for Coulomb potentials. Possible extensions of the result to include broader classes of external potentials and alternative density-like descriptors are discussed.

2773-2778 **Vibrational spectra of an RDX film over an aluminum substrate from molecular dynamics simulations and density functional theory** Julibeth M. Martínez de la Hoz, Perla B. Balbuena [Texas A&M University]

We report calculated vibrational spectra in the range of 0–3,500 cm−1 of RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) molecules adsorbed on a model aluminum surface.

2779-2783 **In pursuit of negative Fukui functions: examples where the highest occupied molecular orbital fails to dominate the chemical reactivity** Eleonora Echegaray, Carlos Cárdenas, Sandra Rabi, Nataly Rabi, Sungmin Lee, Farnaz Heidar Zadeh, Alejandro Toro-Labbe, James S. M. Anderson, Paul W. Ayers[McMaster University,]

In our quest to explore molecules with chemically significant regions where the Fukui function is negative, we explored reactions where the frontier orbital that indicates the sites for electrophilic attack is not the highest occupied molecular orbital.

2785-2790 **A molecular dynamics study on sI hydrogen hydrate** S. Mondal, S. Ghosh, P. K. Chattaraj [Indian Institute of Technology]

A molecular dynamics simulation is carried out to explore the possibility of using sI clathrate hydrate as hydrogen storage material. Metastable hydrogen hydrate structures are generated using the LAMMPS software.

2791-2796 **Assessing modern GGA functionals for solids** Frédéric Labat[Chimie des Interfaces et Modélisation pour l'Énergie,], Eric Brémond, Pietro Cortona, Carlo Adamo

We present periodic calculations carried out with Gaussian-type basis sets on a test set of 21 solids with nine exchange-correlation functionals, extending previous works performed with two parameter-free correlation functionals (TCA and revTCA) which showed promising results for molecules in terms of key structural and energetic properties.

2797-2810 **Computational design of a CNT carrier for a high affinity bispecific anti-HER2 antibody based on trastuzumab and pertuzumab Fabs** Karim Salazar-Salinas, Carlos Kubli-Garfias, Jorge M. Seminario [Texas A&M University]

See Applications / Medicinal Chemistry and Drug Design.

2881-2820 **An intermediate level of approximation for computing the dual descriptor**Jorge Ignacio Martínez-Araya[Universidad Pedro de Valdivia]

At present, there are two levels of approximation to compute the dual descriptor (DD). Between the lowest occupied molecular orbital (LOMO) and the highest unoccupied molecular orbital (HUMO), a framework to provide an expression of the DD in terms of the electronic densities of all molecular orbitals (except HUMO and LOMO) has been proposed to be implemented by programmers as a computational code.

2821-2824 **Pragmatic ab initio prediction of enthalpies of formation for large molecules: accuracy of MP2 geometries and frequencies using CCSD(T) correlation energies** Robert W. Molt Jr., Alexandre Bazanté, Thomas Watson Jr., Rodney J. Bartlett

We have addressed the accuracy of calculating the enthalpy of formation of an arbitrary single reference molecule using practical ab initio methodologies. It is known that MP2 geometries with a triple zeta basis set are almost as reliable as CCSD(T) geometries.

2825-2833 **The average local ionization energy as a tool for identifying reactive sites on defect-containing model graphene systems** Jane S. Murray, Zenaida Peralta-Inga Shields, Pat Lane, Laura Macaveiu, Felipe A. Bulat

In a continuing effort to further explore the use of the average local ionization energy $\bar{I}(r)$ as a computational tool, we have investigated how well $\bar{I}(r)$ computed on molecular surfaces serves as a predictive tool for identifying the sites of the more reactive electrons in several nonplanar defect-containing model graphene systems, each containing one or more pentagons.

2835-2844 **Theoretical description of the magnetic properties of μ3-hydroxo bridged trinuclear copper(II) complexes** Walter Cañon-Mancisidor, Evgenia Spodine, Veronica Paredes-Garcia, Diego Venegas-Yazigi[Universidad de Chile,]

A theoretical study of the magnetic properties, using density functional theory, of a family of trinuclear μ3-OH copper(II) complexes reported in the literature is presented.

In order to understand the charge transfer between the active species, in this work we analyze the influence of the geometry of monoclinic and tetragonal zirconia using reactivity descriptors such as electronic che − mical potential (μ), charge transfer (|ΔN|) and molecular hardness (η).

2893-2900 **Is hyper-hardness more chemically relevant than expected?** Christophe Morell [Université de Lyon], André Grand, Alejandro Toro-Labbé, Henry Chermette

In this work, the third derivative of the energy with respect to the number of electrons, the so-called hyper-hardness, is investigated to assess whether this quantity has a chemical meaning. To achieve this goal a new working expression for hyper-hardness is developed and analyzed.

2901-2911 **Description of local and global shape properties of protein helices** Zhanyong Guo, Elfi Kraka, Dieter Cremer[Southern Methodist University,]

See Methodology / Homology Modeling.

2913-2924 **Assessment of the photosensitization properties of cationic porphyrins in interaction with DNA nucleotide pairs** Gloria I. Cárdenas-Jirón [Universidad de Santiago de Chile (USACH),], Luis Cortez

See Applications / Protein-Nucleic acids.

Journal of Molecular Modeling, 19 (8), August 2013.

2925-2934 **Density functional theory studies of the adsorption of hydrogen sulfide on aluminum doped silicane** Francisco Sánchez-Ochoa, Jonathan Guerrero-Sánchez, Gabriel I. Canto, Gregorio H. Cocoletzi, Noboru Takeuchi [Universidad Nacional Autónoma de México,]

First principles total energy calculations have been performed to study the hydrogen sulfide (H_2S) adsorption on silicane, an unusual one monolayer of Si(111) surface hydrogenated on both sides.

2935-2944 **Computational comparison of the kinetic stabilities of diamino- and diamidocarbenes in the 1,2-H shift reaction** Chin-Hung Lai[Chung Shan Medical University,]

In this study, we performed several DFT, MP2, and BD(T) calculations on the 1,2-H shift reactions of two diaminocarbenes (**1**, **2**) and a diamidocarbene (**3**) using the Gaussian 09 program.

2945-2954 **Theoretical design of energetic nitrogen-rich derivatives of 1,7-diamino-1,7-dinitrimino-2,4,6-trinitro-2,4,6-triazaheptane** Qiong Wu, Weihua Zhu [Nanjing University of Science and Technology,], Heming Xiao

The heats of formation (HOFs), energetic properties, and thermal stability of a series of 1,7-diamino-1,7-dinitrimino-2,4,6-trinitro-2,4,6-triazaheptane derivatives with different substituents, different numbers of substituents, and different original chains are found by using the DFT-B3LYP method.

The energetics of the Menshutkin-like reaction between four mesylate derivatives and ammonia have been computed using B3LYP functional with the 6-31+G** basis set. Additionally, MPW1K/6-31+G** level calculations were carried out to estimate activation barrier heights in the gas phase.

3027-3033 **Quantum-chemical studies on thermodynamic feasibility of 1-methyl-2,4,5-trinitroimidazole processes** Pandurang M. Jadhav [High Energy Materials Research Laboratory (HEMRL),], Radhakrishnan Sarangapani, Vikas D. Ghule, Hima Prasanth, Raj Kishore Pandey

In the present investigations, B3LYP method in combination with 3-21G** basis set has been chosen to evaluate the enthalpy of formation for reaction species by designing reasonable isodesmic reactions. Thermodynamic feasibility of the processes has been worked out assuming free energies of reactions as derived from standard enthalpy and entropy of the reaction species.

3035-3044 **Mechanisms on inhibition of polyethylene electrical tree aging: a theoretical study** Hui Zhang, Yan Shang, Hong Zhao, Baozhong Han, Zesheng Li [Beijing Institute of Technology,]

A theoretical investigation is completed on inhibition mechanism of polyethylene electrical tree aging. Foremost it elucidates that it is one of the important factors for inhibiting initiation and propagation of polyethylene electrical tree through keto-enol tautomerism of acetophenone and its analogues.

3045-3052 **Proteasomal cleavage site prediction of protein antigen using BP neural network based on a new set of amino acid descriptor** Yuanqiang Wang, Yong Lin, Mao Shu, Rui Wang, Yong Hu, Zhihua Lin [Chongqing University of Technology,]

The accurate identification of cytotoxic T lymphocyte epitopes is becoming increasingly important in peptide vaccine design. To enhance the specificity and efficiency of epitope prediction and identification, the recognition mode between the ubiquitin–proteasome complex and the protein antigen must be considered. This study proposes a new set of parameters to characterize the cleavage window and uses a backpropagation neural network algorithm to build a model that accurately predicts proteasomal cleavage.

3053-3064 **Gene identification and comparative molecular modeling of a *Trypanosoma rangeli* major surface protease** Paulo H. M. Calixto, Mainá Bitar, Keila A. M. Ferreira, Odonírio Abrahão Jr., Eliane Lages-Silva,Glória R. Franco, Luis E. Ramírez, André L. Pedrosa [Universidade Federal do Triângulo Mineiro,

See Applications / Homology Modeling.

3065-3075 **Density functional study of structural and electronic properties of small binary $Be_nCu_m(n+m=2\sim7)$ clusters** Si-Cheng Li, Ying Li, Di Wu [Jilin University,], Zhi-Ru Li

The geometrical structures, electronic properties and relative stabilities of small bimetallic $Be_nCu_m(n+m=2–7)$ clusters have been systematically investigated by using a density functional method at the B3PW91 level. In the most stable structures of Be_nCu_m, the Be atoms tend to gather together and construct similar configurations to those of pure Be_n clusters.

3077-3086 **High-spin binuclear cyclopentadienyliron chlorides: a density functional theory study** Congzhi Wang, Xiuhui Zhang, Yang Bai, Fengxin Gao, Qianshu Li Beijing Institute of Technology,]

Theoretical studies on the cyclopentadienyliron chlorides $Cp_2Fe_2Cl_n (n = 6 - 1)$ with iron in the formal oxidation states from +1 to +4 indicate that all the high-spin species are predicted to be the lowest energy structures and they are paramagnetic complexes with magnetic moments between $2.8\mu_B$ and $5.9\mu_B$.

3087-3094 **Insight into the binding model of new antagonists of kappa receptor using docking and molecular dynamics simulation** Shiyuan Hu, Haijing Yu, Yongjuan Liu, Tian Xue, Huabei Zhang [Beijing Normal University]

See Applications / Ligand Binding.

3095-3102 **Electron correlation effects and density analysis of the first-order hyperpolarizability of neutral guanine tautomers** Andrea Alparone [University of Catania,]

Dipole moments (μ), charge distributions, and static electronic first-order hyperpolarizabilities (β_μ) of the two lowest-energy keto tautomers of guanine (**7H** and **9H**) were determined in the gas phase using Hartree–Fock, Møller–Plesset perturbation theory (MP2 and MP4), and DFT (PBE1PBE, B97-1, B3LYP, CAM-B3LYP) methods with Dunning's correlation-consistent aug-cc-pVDZ and *d*-aug-cc-pVDZ basis sets.

3103-3118 **Theoretical studies of energetic nitrogen-rich ionic salts composed of substituted 5-nitroiminotetrazolate anions and various cations** Fang Xiang, Weihua Zhu [Nanjing University of Science and Technology,], Heming Xiao

We have performed density functional theory and volume-based thermodynamics calculations to study the effects of different combinations of energetic anions and cations on the crystal densities, heats of formation, energetic properties, and thermodynamics of formation for a series of 5-nitroiminotetrazolate-based ionic salts.

3119-3125 **Structural transitions in mixed ternary noble gas clusters** Xia Wu [Anqing Normal University,], Yan Sun, Yin-Chun Gao, Gen-Hua Wu

The properties of noble gas systems can be greatly extended by heterogeneous mixtures of elements. The geometrical structures and energies of mixed Ar–Kr–Xe clusters were investigated using ternary Lennard-Jones (TLJ) potential. For the $Ar_{19}Kr_nXe_{19}$, $Ar_{19}Kr_{19}Xe_n$, and $Ar_nKr_{19}Xe_{19}$ ($n = 0$–17) clusters investigated, the results show that only two minimum energy configurations exist, i.e., polytetrahedron and six-fold pancake.

3127-3134 **Density functional theory study of epoxy polymer chains adsorbing onto single-walled carbon nanotubes: electronic and mechanical properties** Morteza Ghorbanzadeh Ahangari [Islamic Azad University], Abdolhosein Fereidoon, Masoud Darvish Ganji

We performed first principles calculations based on density functional theory (DFT) to investigate the effect of epoxy monomer content on the electronic and mechanical properties of single-walled carbon nanotubes (SWCNTs). Our calculation results reveal that interfacial interaction increases with increasing numbers of epoxy monomers on the surface of SWCNTs.

release of the bromide anion and a radical. Both the geometry and energy of the BDE-21 neutral and its possible anionic states were studied.

3339-3349 **Structural and energetic properties of canonical and oxidized telomeric complexes studied by molecular dynamics simulations** Przemysław Czeleń [Nicolaus Copernicus University in Toruń,], Piotr Cysewski

See Applications / Protein Dynamics.

3351-3367 **Insight into the 3D structure of ADP-glucose pyrophosphorylase from rice (*Oryza sativa* L.)** Chhavi Dawar, Sunita Jain, Sudhir Kumar [CCS Haryana Agricultural University]

See Applications / Homology Modeling.

3369-3383 **Sequence and structural investigation of a novel psychrophilic α-amylase from*Glaciozyma antarctica* PI12 for cold-adaptation analysis** Aizi Nor Mazila Ramli, Mohd Akmal Azhar, Mohd Shahir Shamsir, Amir Rabu, Abdul Munir Abdul Murad, Nor Muhammad Mahadi, Rosli Md. Illias [Universiti Teknologi Malaysia]

See Applications / Protein Structure Analysis.

3385-3396 **Rational synthesis of pindolol imprinted polymer by non-covalent protocol based on computational approach** Kiran Kumar Tadi, Ramani V. Motghare[Visvesvaraya National Institute of Technology, Nagpur]

In the present work, *ab initio* quantum mechanical simulations and computational screening were used to identify functional monomer having best interactions with PDL. A virtual library of 16 functional monomers was built and the possible minimum energy conformation of the monomers and PDL were calculated using Hartree-Fock (HF) method for the synthesis of PDL imprinted polymer.

3397-3402 **Effect of benzoannulation on tautomeric preferences of 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione** Robert Dobosz [University of Technology and Life Sciences, Seminaryjna], Ryszard Gawinecki

Density functional theory (DFT) calculations at the B3LYP/6-311+G(d,p) level show that 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione is a labile compound. On the other hand, its dienolimine tautomer (4,6-di(pyridin-2-yl)cyclohaxa-1,3-diene-1,3-diol) seems stable enough to be present in vacuum.

3403-3410 **Comparative theoretical studies of energetic pyrazole-pyridine derivatives** Guo-zheng Zhao, Ming Lu [Nanjing University of Science & Technology]

The pyrazole-pyridine derivatives were optimized to obtain their molecular geometries and electronic structures at the DFT-B3LYP/6-31G(d,p) and DFT-B3P86/6-31G(d,p) levels. Molecular mechanics (MM) calculations were performed for the title compounds.

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1. APPLICATIONS

1.1. *Small Molecules*

General and Model System

Systematic Improvement of a Classical Molecular Model of Water

Lee-Ping Wang, Teresa Head-Gordon, Jay W. Ponder, Pengyu Ren, John D. Chodera, Peter K. Eastman, Todd J. Martinez, and Vijay S. Pande [Stanford University]

J. Phys. Chem. B., **117**, 9956–9972, 2013**.**

The model is parameterized using ForceBalance, a systematic optimization method that simultaneously utilizes training data from experimental measurements and high-level *ab initio* calculations. We show that iAMOEBA is a highly accurate model for water in the solid, liquid, and gas phases, with the ability to fully capture the effects of electronic polarization and predict a comprehensive set of water properties beyond the training data set including the phase diagram.

Water and solvation

Mechanisms of Acceleration and Retardation of Water Dynamics by Ions

Guillaume Stirnemann, Erik Wernersson, Pavel Jungwirth, and Damien Laage [Ecole Normale Supérieure]

J. Am. Chem. Soc., 2013, **135**, 11824–11831

There are fundamental and not yet fully resolved questions concerning the impact of solutes, ions in particular, on the structure and dynamics of water, which can be formulated as follows: Are the effects of ions local or long-ranged? Is the action of cations and anions on water cooperative or not? Here, we investigate how the reorientation and hydrogen-bond dynamics of water are affected by ions in dilute and concentrated aqueous salt solutions. By combining simulations and analytic modeling, we first show that ions have a short-ranged influence on the reorientation of individual water molecules and that depending on their interaction strength with water, they may accelerate or slow down water dynamics.

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Dr. David Busath edited volumes 7-14

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Water and Solvation (Cont'd)

Polarizable Water Models from Mixed Computational and Empirical Optimization

Philipp Tröster, Konstantin Lorenzen, Magnus Schwörer, and Paul Tavan [Universität München]

J. Phys. Chem. B., **117**, 9486-9500, 2013**.**

The computational part of the parameter optimization relies on hybrid calculations combining density functional theory (DFT) for a solute molecule with a PMM treatment of its solvent environment at well-defined thermodynamic conditions. As an application we have developed PMM models for water featuring $\nu = 3$, 4, and 5 points of force action, a Gaussian inducible dipole and a Buckingham potential at the oxygen, the experimental liquid phase geometry, the experimental gas phase polarizability $\alpha_{exp}^{g} = 1.47$ Å ^{3}, and, for $\nu = 4$ and 5, the gas phase value $\mu_{exp}^{g} = 1.855$ D for the static dipole moment.

Organic Solvents

Development of Dimethyl Sulfoxide Solubility Models Using 163 000 Molecules: Using a Domain Applicability Metric to Select More Reliable Predictions

Igor V. Tetko[Helmholtz Zentrum München—German Research Center for Environmental Health (GmbH)], Sergii Novotarskyi, Iurii Sushko, Vladimir Ivanov, Alexander E. Petrenko, Reiner Dieden, Florence Lebon, and Benoit Mathieu

J.Chem. Infor. and Mod. **53**, 1990–2000, 2013.

The dimethyl sulfoxide (DMSO) solubility data from Enamine and two UCB pharma compound collections were analyzed using 8 different machine learning methods and 12 descriptor sets. The analyzed data sets were highly imbalanced with 1.7–5.8% nonsoluble compounds. The libraries' enrichment by soluble molecules from the set of 10% of the most reliable predictions was used to compare prediction performances of the methods. The highest accuracies were calculated using a C4.5 decision classification tree, random forest, and associative neural networks.

Medicinal Chemistry and Drug Design

Autotaxin inhibition: Development and application of computational tools to identify site-selective lead compounds

Derek D. Norman, Ayolah Ibezim, Whitney E. Scott, Stanley White, Abby L. Parrill, Daniel L. Baker [The University of Memphis]

Bioorg. and Med.Chem., **21**, 5548-5560, 2013.

Autotaxin (ATX) catalyzes the conversion of lysophosphatidyl choline (LPC) to lysophosphatidic acid (LPA). Both ATX and LPA have been linked to pathophysiologies ranging from cancer to neuropathic pain. Inhibition of LPA production by ATX is therefore of therapeutic interest. Here we report the application of previously-developed, subsite-targeted pharmacophore models in a screening workflow that involves either docking or binary QSAR as secondary filters to identify ATX inhibitors from previously unreported structural types, four of which have sub-micromolar inhibition constants.

Medicinal Chemistry and Drug Design (Cont'd)

Design and synthesis of novel series of 5-HT_6 receptor ligands having indole, a central aromatic core and 1-amino-4 methyl piperazine as a positive ionizable group

Faisal Hayat, Sungjin Cho, Hyewhon Rhim, Ambily Nath Indu Viswanath, Ae Nim Pae, Jae Yeol Lee, Dong Joon Choo, Hea-Young Park Choo[Ewha Womans University]

Bioorg. and Med.Chem., **21**, 5573-5582, 2013.

Based on a pharmacophore model reported in the literature, we designed and synthesized a novel series of 5-HT_6receptor ligands having indole as a central aromatic core and 1-amino-4-methyl piperazine as positive ionizable group.Out of 32 compounds we have successfully identified 10 new compounds as 5-HT_6 receptor antagonists. The structure–activity relationship (SAR) studies have been carried out by mapping the compounds with the 3D QSAR model.

Synthesis, enzyme kinetics and computational evaluation of N-(β-D-glucopyranosyl) oxadiazolecarboxamides as glycogen phosphorylase inhibitors

Mária Polyák, Gergely Varga, Bence Szilágyi, László Juhász, Tibor Docsa, Pál Gergely, Jaida Begum, Joseph M. Hayes, László Somsák [University of Debrecen]

Bioorg. and Med.Chem., **21**, 5738-5747, 2013.

S!

All possible isomers of *N*-β-D-glucopyranosyl aryl-substituted oxadiazolecarboxamides were synthesised. *O*-Peracetylated *N*-cyanocarbonyl-β-D-glucopyranosylamine was transformed into the corresponding *N*-glucosyl tetrazole-5-carboxamide, which upon acylation gave *N*-glucosyl 5-aryl-1,3,4-oxadiazole-2-carboxamides. The nitrile group of the *N*-cyanocarbonyl derivative was converted to amidoxime which was ring closed by acylation to *N*-glucosyl 5-aryl-1,2,4-oxadiazole-3-carboxamides. A one-pot reaction of protected β-D-glucopyranosylamine with oxalyl chloride and then with arenecarboxamidoximes furnished *N*-glucosyl 3-aryl-1,2,4-oxadiazole-5-carboxamides.

Spectroscopic, computational modeling and cytotoxicity of a series of meso-phenyl and meso-thienyl-BODIPYs

Jaime H. Gibbs, Larry T. Robins, Zehua Zhou, Petia Bobadova-Parvanova, Michael Cottam, Gregory T. McCandless, Frank R. Fronczek, M. Graça H. Vicente [Louisiana State University]

Bioorg. and Med.Chem., **21**, 5770-5781, 2013.

A series of twenty-two BODIPY compounds were synthesized, containing various *meso*-phenyl and *meso*-thienyl groups, and their spectroscopic and structural properties were investigated using both experimental and computational methods. Further functionalization of the BODIPY framework via iodination at the 2,6-pyrrolic positions was explored in order to determine the effect of these heavy atoms on the photophysical and cytotoxicity of the *meso*-aryl-BODIPYs. BODIPYs bearing *meso*-thienyl substituents showed the largest red-shifted absorptions and emissions and reduced fluorescence quantum yields.

Structure guided inhibitor designing of CDK2 and discovery of potential leads against cancer

Arun Kumar V.A [Sathyabama University], Keshav Mohan, Syed Riyaz

J. Mol.Mod., **19,** 3581-3589, 2013.

S!

On the basis of stereo specific information obtained from crystal structures of CDK2, indole and chromene analogues were designed by suitably substituting the pharmacophores on their moiety and docked with target protein for calculating binding affinities. The binding affinities are represented in glide score. (5*E*)-5-[(1-methyl-1*H*-indol-3-yl)methylidene]-2,4,6-trioxotetrahydro-2*H*-pyrimidin-1-ide (I_1), (5*E*)-5-(1*H*-indol-3-ylmethylidene)-2,4,6-trioxotetrahydro-2*H*-pyrimidin-1-ide (I_2) and 2-amino-4-(4-methyl phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (C_9) were selected for synthesis and biological testing based on vital interactions.

Medicinal Chemistry and Drug Design (Cont'd)

Computationally designed prodrugs of statins based on Kirby's enzyme model

Rafik Karaman [University of Basilicata], Wajd Amly, Laura Scrano, Gennaro Mecca, Sabino A. Bufo

J. Mol.Mod., **19,** 3969-3982, 2013.

DFT calculations at B3LYP/6-31G(d,p) for intramolecular proton transfer in Kirby's enzyme models**1**–**7** demonstrated that the reaction rate is dependent on the distance between the two reacting centers, r_{GM}, and the hydrogen bonding angle, α, and the rate of the reaction is linearly correlated with r_{GM} and α. Based on these calculation results three simvastatin prodrugs were designed with the potential to provide simvastatin with higher bioavailability.

Vinyl Sulfone-Based Peptidomimetics as Anti-Trypanosomal Agents: Design, Synthesis, Biological and Computational Evaluation

Elizabeth Dunny, William Doherty, Paul Evans, J. Paul G. Malthouse, Derek Nolan, and Andrew J. S. Knox [Trinity College Dublin]

J.Med.Chem., **56,** 6638–6650, 2013.

A series of vinyl sulfone-containing peptidomimetics were rationally designed, synthesized, and evaluated against *Trypanosoma brucei brucei*. These electrophilic compounds are likely to exert their antitrypanosomal activity via inhibition of trypanosomal cysteine proteases, TbCatB and rhodesain, through alkylation of a key cysteine residue within the protease active site. The series was designed to present complementary groups to naturally recognized peptide substrates while probing tolerance to a range of substitutions at the P1, P1′, and P2 positions. The most potent compound, **29** (EC_{50} = 70 nM, *T. b. brucei* whole cell assay), displayed minimal toxicity (>785 times selectivity) when assayed for cytotoxicity against the human promyelocytic leukemia (HL-60) cell line.

New Anticancer Agents Mimicking Protein Recognition Motifs

Marco Persico, Anna Ramunno, Vita Maglio, Silvia Franceschelli, Chiara Esposito, Alfonso Carotenuto, Diego Brancaccio, Valeria De Pasquale, Luigi Michele Pavone, Michela Varra, Nausicaa Orteca, Ettore Novellino, and Caterina Fattorusso [Università di Napoli "Federico II"]

J.Med.Chem., **56,** 6666–6680, 2013.

The novel tetrasubstituted pyrrole derivatives **8g**, **8h**, and **8i** showed selective cytotoxicity against M14 melanoma cells at low micromolar concentration. Structure–activity relationships (SARs) indicated the presence of three aromatic substituents on the pyrrole core as necessary for biological activity. Computational studies strongly suggest that the peculiar 3D orientation of these substituents is able to reproduce the hydrophobic side chains in LxxLL-like protein recognition motifs. Biological results showed altered p53 expression and nuclear translocation in cells sensitive to the compounds, suggesting p53 involvement in their anticancer mechanism of action.

Acetylcholinesterase Inhibitors: Structure Based Design, Synthesis, Pharmacophore Modeling, and Virtual Screening

Koteswara Rao Valasani, Michael O. Chaney, Victor W. Day, and Shirley ShiDu Yan [University of Kansas]

J.Chem. Infor. and Mod. **53**, 2033-2046, 2013.

Acetylcholinesterase (AChE) is a main drug target, and its inhibitors have demonstrated functionality in the symptomatic treatment of Alzheimer's disease (AD). In this study, a series of novel AChE inhibitors were designed and their inhibitory activity was evaluated with 2D quantitative structure–activity relationship (QSAR) studies using a training set of 20 known compounds for which IC_{50} values had previously been determined. The QSAR model was calculated based on seven unique descriptors. Model validation was determined by predicting IC_{50} values for a test set of 20 independent compounds with measured IC_{50} values.

Medicinal Chemistry and Drug Design (Cont'd)

Discovery and Design of Tricyclic Scaffolds as Protein Kinase CK2 (CK2) Inhibitors through a Combination of Shape-Based Virtual Screening and Structure-Based Molecular Modification

Haopeng Sun, Xiaoli Xu, Xiaowen Wu, Xiaojin Zhang, Fang Liu, Jianmin Jia, Xiaoke Guo, Jingjie Huang, Zhengyu Jiang, Taotao Feng, Hongxi Chu, You Zhou, Shenglie Zhang, Zongliang Liu, and Qidong You [China Pharmaceutical University]

J.Chem. Infor. and Mod. **53**, 2093-2102, 2013.

Protein kinase CK2 (CK2), a ubiquitous serine/threonine protein kinase for hundreds of endogenous substrates, serves as an attractive anticancer target. One of its most potent inhibitors, CX-4945, has entered a phase I clinical trial. Herein we present an integrated workflow combining shape-based virtual screening for the identification of novel CK2 inhibitors. A shape-based model derived from CX-4945 was built, and the subsequent virtual screening led to the identification of several novel scaffolds with high shape similarity to that of CX-4945.

S! & A!

Structure–Activity Relationships in Non-Ligand Binding Pocket (Non-LBP) Diarylhydrazide Antiandrogens

Laura Caboni, Billy Egan, Brendan Kelly, Fernando Blanco, Darren Fayne, Mary J. Meegan, and David G. Lloyd [Trinity Biomedical Sciences Institute]

J.Chem. Infor. and Mod. **53**, 2116–2130, 2013.

We report the synthesis and a study of the structure–activity relationships of a new series of diarylhydrazides as potential selective non-ligand binding pocket androgen receptor antagonists. Their biological activity as antiandrogens in the context of the development of treatments for castration resistant prostate cancer was evaluated using *in vitro* time resolved fluorescence resonance energy transfer and fluorescence polarization on target assays.

Relating Anatomical Therapeutic Indications by the Ensemble Similarity of Drug Sets

Leihong Wu, Ni Ai, Yufeng Liu, Yi Wang, and Xiaohui Fan [Zhejiang University]

J.Chem. Infor. and Mod. **53**, 2154–2160, 2013.

Our study demonstrated that iSEA was capable of relating ATC classes, and these relationships could accurately assign the right indications for approved drugs and make reasonable predictions about possible clinical indications for unclassified drugs, which would provide valuable information for drug repositioning.

Quantitative Structure-Activity Relations

Comprehensive 3D-QSAR and binding mode of BACE-1 inhibitors using R-group search and molecular docking

Dandan Huang, Yonglan Liu, Bozhi Shi, Yueting Li, Guixue Wang, Guizhao Liang [Chongqing University]

J. Mol.Graph. and Mod., **45,** 65–83, 2013.

The β-enzyme (BACE), which takes an active part in the processing of amyloid precursor protein, thereby leads to the production of amyloid-β (Aβ) in the brain, is a major therapeutic target against Alzheimer's disease. The present study is aimed at studying 3D-QSAR of BACE-1 inhibitors and their binding mode. We build a 3D-QSAR model involving 99 training BACE-1 inhibitors based on Topomer CoMFA, and 26 molecules are employed to validate the external predictive power of the model obtained.

Quantitative Structure-Activity Relations (Cont'd)

Predicting Binding Affinity of CSAR Ligands Using Both Structure-Based and Ligand-Based Approaches

Denis Fourches, Eugene Muratov, Feng Ding, Nikolay V. Dokholyan, and Alexander Tropsha[University of North Carolina]

J.Chem. Infor. and Mod. **53**, 1915–1922, 2013.

We report on the prediction accuracy of ligand-based (2D QSAR) and structure-based (MedusaDock) methods used both independently and in consensus for ranking the congeneric series of ligands binding to three protein targets (UK, ERK2, and CHK1) from the CSAR 2011 benchmark exercise. An ensemble of predictive QSAR models was developed using known binders of these three targets extracted from the publicly available ChEMBL database. Selected models were used to predict the binding affinity of CSAR compounds toward the corresponding targets and rank them accordingly; the overall ranking accuracy evaluated by Spearman correlation was as high as 0.78 for UK, 0.60 for ERK2, and 0.56 for CHK1, placing our predictions in the top 10% among all the participants.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

A computational method to preclude multistationarity in networks of interacting species

Elisenda Feliu and Carsten Wiuf [University of Copenhagen]

Bioinformatics. **29**, 2327-2334, 2013.

Modeling and analysis of complex systems are important aspects of understanding systemic behavior. We have developed and implemented a method to decide whether any ODE model in a given class cannot have multiple steady states. The method runs efficiently on models of moderate size. We tested the method on a large set of models for gene silencing by sRNA interference and on two publicly available databases of biological models, KEGG and Biomodels.

iLoops: a protein–protein interaction prediction server based on structural features

Joan Planas-Iglesias, Manuel A. Marin-Lopez, Jaume Bonet, Javier Garcia-Garcia, and Baldo Oliva [Universitat Pompeu Fabra]

Bioinformatics. **29**, 2360-2362, 2013.

Protein–protein interactions play a critical role in many biological processes. Despite that, the number of servers that provide an easy and comprehensive method to predict them is still limited. Here, we present iLoops, a web server that predicts whether a pair of proteins can interact using local structural features. The inputs of the server are as follows: (i) the sequences of the query proteins and (ii) the pairs to be tested. Structural features are assigned to the query proteins by sequence similarity.

Bioinformatics and Cheminformatics (Cont'd)

A parallel finite element simulator for ion transport through three-dimensional ion channel systems

Bin Tu, Minxin Chen, Yan Xie, Linbo Zhang, Bob Eisenberg, Benzhuo Lu [Chinese Academy of Sciences, Beijing]

J. Comp. Chem., **34**, 2065–2078, 2013.

A parallel finite element simulator, ichannel, is developed for ion transport through three-dimensional ion channel systems that consist of protein and membrane. The coordinates of heavy atoms of the protein are taken from the Protein Data Bank and the membrane is represented as a slab. The simulator contains two components: a parallel adaptive finite element solver for a set of Poisson–Nernst–Planck (PNP) equations that describe the electrodiffusion process of ion transport, and a mesh generation tool chain for ion channel systems, which is an essential component for the finite element computations.

GALAMOST: GPU-accelerated large-scale molecular simulation toolkit

You-Liang Zhu, Hong Liu, Zhan-Wei Li,Hu-Jun Qian, Giuseppe Milano, Zhong-Yuan Lu [Jilin University]

J. Comp. Chem., **34**, 2197–2211, 2013.

GALAMOST graphics processing unit (GPU)-accelerated large-scale molecular simulation toolkit] is a molecular simulation package designed to utilize the computational power of GPUs. Besides the common features of molecular dynamics (MD) packages, it is developed specially for the studies of self-assembly, phase transition, and other properties of polymeric systems at mesoscopic scale by using some lately developed simulation techniques. To accelerate the simulations, GALAMOST contains a hybrid particle-field MD technique where particle–particle interactions are replaced by interactions of particles with density fields.

VinaMPI: Facilitating multiple receptor high-throughput virtual docking on high-performance computers

Sally R. Ellingson, Jeremy C. Smith, Jerome Baudry [University of Tennessee]

J. Comp. Chem., **34**, 2212–2221, 2013.

The program VinaMPI has been developed to enable massively large virtual drug screens on leadership-class computing resources, using a large number of cores to decrease the time-to-completion of the screen. VinaMPI is a massively parallel Message Passing Interface (MPI) program based on the multithreaded virtual docking program AutodockVina, and is used to distribute tasks while multithreading is used to speed-up individual docking tasks.

Selectivity Data: Assessment, Predictions, Concordance, and Implications

Cen Gao, Suntara Cahya, Christos A. Nicolaou, Jibo Wang, Ian A. Watson, David J. Cummins, Philip W. Iversen, and Michal Vieth [Lilly Research Laboratories]

J.Med.Chem., **56,** 6991–7002, 2013.

For molecules that are either highly selective or potent, the concordance between different experimental sources is significantly higher than the concordance between experimental and predicted values. We also show that computational models built from one data set are less predictive for other data sources and highlight the importance of bias correction for assessing selectivity data. Finally, we show that small-molecule target space relationships derived from different data sources and predictive models share overall similarity but can significantly differ in details.

Bioinformatics and Cheminformatics (Cont'd)

Ranking multiple docking solutions based on the conservation of inter-residue contacts

Romina Oliva [University "Parthenope" of Naples], Anna Vangone and Luigi Cavallo

Proteins: Stru. Fun. & Bioinf., **81**, 1571–1584, 2013.

Molecular docking is the method of choice for investigating the molecular basis of recognition in a large number of functional protein complexes. However, correctly scoring the obtained docking solutions (decoys) to rank native-like (NL) conformations in the top positions is still an open problem. Herein we present CONSRANK, a simple and effective tool to rank multiple docking solutions, which relies on the conservation of inter-residue contacts in the analyzed decoys ensemble.

CSAR Data Set Release 2012: Ligands, Affinities, Complexes, and Docking Decoys

James B. Dunbar [University of Michigan], Jr., Richard D. Smith, Kelly L. Damm-Ganamet, Aqeel Ahmed, Emilio Xavier Esposito, James Delproposto, Krishnapriya Chinnaswamy, You-Na Kang, Ginger Kubish, Jason E. Gestwicki, Jeanne A. Stuckey, and Heather A. Carlson

J.Chem. Infor. and Mod. **53**, 1842-1852, 2013.

A major goal in drug design is the improvement of computational methods for docking and scoring. The Community Structure Activity Resource (CSAR) has collected several data sets from industry and added in-house data sets that may be used for this purpose (www.csardock.org). CSAR has currently obtained data from Abbott, GlaxoSmithKline, and Vertex and is working on obtaining data from several others. Combined with our in-house projects, we are providing a data set consisting of 6 protein targets, 647 compounds with biological affinities, and 82 crystal structures.

S!

CSAR Benchmark Exercise 2011–2012: Evaluation of Results from Docking and Relative Ranking of Blinded Congeneric Series

Kelly L. Damm-Ganamet, Richard D. Smith, James B. Dunbar, Jr., Jeanne A. Stuckey, and Heather A. Carlson [University of Michigan]

J.Chem. Infor. and Mod. **53**, 1853-1870, 2013.

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The exercise was built around blinded high-quality experimental data from four protein targets: LpxC, Urokinase, Chk1, and Erk2. Pose prediction proved to be the most straightforward task, and most methods were able to successfully reproduce binding poses when the crystal structure employed was co-crystallized with a ligand from the same chemical series. Multiple evaluation metrics were examined, and we found that RMSD and native contact metrics together provide a robust evaluation of the predicted poses.

Incorporating Backbone Flexibility in MedusaDock Improves Ligand-Binding Pose Prediction in the CSAR2011 Docking Benchmark

Feng Ding and Nikolay V. Dokholyan[University of North Carolina at Chapel Hill]

J.Chem. Infor. and Mod. **53**, 1871-1849, 2013.

Solution of the structures of ligand–receptor complexes via computational docking is an integral step in many structural modeling efforts as well as in rational drug discovery. A major challenge in ligand–receptor docking is the modeling of both receptor and ligand flexibilities in order to capture receptor conformational changes induced by ligand binding. In the molecular docking suite MedusaDock, both ligand and receptor *side chain* flexibilities are modeled simultaneously with sets of discrete rotamers, where the ligand rotamer library is generated "on the fly" in a stochastic manner.

Bioinformatics and Cheminformatics (Cont'd)

Investigation on the Effect of Key Water Molecules on Docking Performance in CSARdock Exercise

Ashutosh Kumar and Kam Y. J. Zhang [Zhang Initiative Research Unit]

J.Chem. Infor. and Mod. **53**, 1880-1892, 2013.

Our study showed that water mapping calculations can be used to select key water molecules from experimentally identified water positions for molecular dockings. We have observed that inclusion of all binding site water molecules led to reduced performance and erroneous results. Moreover, an overall improvement in binding pose prediction was achieved when computationally selected water molecules are included during docking simulations.

Lessons Learned in Empirical Scoring with smina from the CSAR 2011 Benchmarking Exercise

David Ryan Koes [University of Pittsburgh], Matthew P. Baumgartner, and Carlos J. Camacho

J.Chem. Infor. and Mod. **53**, 1893–1904, 2013.

We describe a general methodology for designing an empirical scoring function and provide smina, a version of AutoDock Vina specially optimized to support high-throughput scoring and user-specified custom scoring functions. Using our general method, the unique capabilities of smina, a set of default interaction terms from AutoDock Vina, and the CSAR (Community Structure–Activity Resource) 2010 data set, we created a custom scoring function and evaluated it in the context of the CSAR 2011 benchmarking exercise.

Automated Large-Scale File Preparation, Docking, and Scoring: Evaluation of ITScore and STScore Using the 2012 Community Structure–Activity Resource Benchmark

Sam Z. Grinter, Chengfei Yan, Sheng-You Huang, Lin Jiang, and Xiaoqin Zou [University of Missouri]

J.Chem. Infor. and Mod. **53**, 1905–1914, 2013.

In this study, we use the recently released 2012 Community Structure–Activity Resource (CSAR) data set to evaluate two knowledge-based scoring functions, ITScore and STScore, and a simple force-field-based potential (VDWScore). The CSAR data set contains 757 compounds, most with known affinities, and 57 crystal structures. With the help of the script files for docking preparation, we use the full CSAR data set to evaluate the performances of the scoring functions on binding affinity prediction and active/inactive compound discrimination.

SFCscore^{RF}: A Random Forest-Based Scoring Function for Improved Affinity Prediction of Protein–Ligand Complexes

David Zilian and Christoph A. Sotriffer [University of Wuerzburg, Am Hubland]

J.Chem. Infor. and Mod. **53**, 1923–1933, 2013.

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Herein, we describe the use of SFCscore descriptors to develop an improved scoring function by means of a PDBbind training set of 1005 complexes in combination with random forest for regression. This provided SFCscore^{RF} as a new scoring function with significantly improved performance on the PDBbind and CSAR–NRC HiQ benchmarks in comparison to previously developed SFCscore functions.

Application of the Docking Program SOL for CSAR Benchmark

Alexey V. Sulimov, Danil C. Kutov, Igor V. Oferkin, Ekaterina V. Katkova, and Vladimir B. Sulimov [Moscow State University]

J.Chem. Infor. and Mod. **53**, 1946–1956, 2013.

This paper is devoted to results obtained by the docking program SOL and the post-processing program DISCORE at the CSAR benchmark. SOL and DISCORE programs are described. SOL is the original docking program developed on the basis of the genetic algorithm, MMFF94 force field, rigid protein, precalculated energy grid including desolvation in the frame of simplified GB model, vdW, and electrostatic interactions and taking into account the ligand internal strain energy.

Bioinformatics and Cheminformatics (Cont'd)

In Silico Target Predictions: Defining a Benchmarking Data Set and Comparison of Performance of the Multiclass Naïve Bayes and Parzen-Rosenblatt Window

Alexios Koutsoukas, Robert Lowe, Yasaman KalantarMotamedi, Hamse Y. Mussa, Werner Klaffke, John B. O. Mitchell, Robert C. Glen[University of Cambridge], and Andreas Bender

J.Chem. Infor. and Mod. **53**, 1957–1966, 2013.

In this study, two probabilistic machine-learning algorithms were compared for in silico target prediction of bioactive molecules, namely the well-established Laplacian-modified Naïve Bayes classifier (NB) and the more recently introduced (to Cheminformatics) Parzen-Rosenblatt Window. Both classifiers were trained in conjunction with circular fingerprints on a large data set of bioactive compounds extracted from ChEMBL, covering 894 human protein targets with more than 155,000 ligand-protein pairs. This data set is also provided as a benchmark data set for future target prediction methods due to its size as well as the number of bioactivity classes it contains.

Enhancing Molecular Shape Comparison by Weighted Gaussian Functions

Xin Yan, Jiabo Li, Zhihong Liu, Minghao Zheng, Hu Ge, and Jun Xu [Sun Yat-sen University]

J.Chem. Infor. and Mod. **53**, 1967–1978, 2013.

Shape comparing technologies based on Gaussian functions have been widely used in virtual screening of drug discovery. For efficiency, most of them adopt the First Order Gaussian Approximation (FOGA), in which the shape density of a molecule is represented as a simple sum of all individual atomic shape densities. In the current work, the effectiveness and error in shape similarity calculated by such an approximation are carefully analyzed. A new approach, which is called the Weighted Gaussian Algorithm (WEGA), is proposed to improve the accuracy of the first order approximation.

SMIfp (SMILES fingerprint) Chemical Space for Virtual Screening and Visualization of Large Databases of Organic Molecules

Julian Schwartz, Mahendra Awale, and Jean-Louis Reymond [University of Berne]

J.Chem. Infor. and Mod. **53**, 1979–1989, 2013.

SMIfp (SMILES fingerprint) is defined here as a scalar fingerprint describing organic molecules by counting the occurrences of 34 different symbols in their SMILES strings, which creates a 34-dimensional chemical space. Ligand-based virtual screening using the city-block distance CBD_{SMIfp} as similarity measure provides good AUC values and enrichment factors for recovering series of actives from the directory of useful decoys (DUD-E) and from ZINC. DrugBank, ChEMBL, ZINC, PubChem, GDB-11, GDB-13, and GDB-17 can be searched by CBD_{SMIfp} using an online SMIfp-browser at www.gdb.unibe.ch.

Accelerated Conformational Entropy Calculations Using Graphic Processing Units

Qian Zhang, Junmei Wang, Ginés D. Guerrero, José M. Cecilia, José M. García, Youyong Li, Horacio Pérez-Sánchez, and Tingjun Hou [Zhejiang University]

J.Chem. Infor. and Mod. **53**, 1017–1025, 2013.

Conformational entropy calculation, usually computed by normal-mode analysis (NMA) or quasi harmonic analysis (QHA), is extremely time-consuming. Here, instead of NMA or QHA, a solvent accessible surface area (SASA) based model was employed to compute the conformational entropy, and a new fast GPU-based method called MURCIA (Molecular Unburied Rapid Calculation of Individual Areas) was implemented to accelerate the calculation of SASA for each atom. MURCIA employs two different kernels to determine the neighbors of each atom.

Bioinformatics and Cheminformatics (Cont'd)

SimG: An Alignment Based Method for Evaluating the Similarity of Small Molecules and Binding Sites

Chaoqian Cai, Jiayu Gong, Xiaofeng Liu, Daqi Gao, and Honglin Li [East China University of Science and Technology]

J.Chem. Infor. and Mod. **53**, 2103–2115, 2013.

In this study, a Gaussian volume overlap and chemical feature based molecular similarity metric was devised, and a downhill simplex searching was carried out to evaluate the corresponding similarity. By representing the shapes of both the candidate small molecules and the binding site with chemical features and comparing the corresponding Gaussian volumes overlaps, the active compounds could be identified. These two aspects compose the proposed method named SimG which supports both structure-based and ligand-based strategies.

Protein Structure prediction

Enhanced hybrid search algorithm for protein structure prediction using the 3D-HP lattice model

Changjun Zhou [Dalian University], Caixia Hou, Qiang Zhang, Xiaopeng Wei

J. Mol.Mod., **19,** 3883-3891, 2013.

The problem of protein structure prediction in the hydrophobic-polar (HP) lattice model is the prediction of protein tertiary structure. This problem is usually referred to as the protein folding problem. This paper presents a method for the application of an enhanced hybrid search algorithm to the problem of protein folding prediction, using the three dimensional (3D) HP lattice model. The enhanced hybrid search algorithm is a combination of the particle swarm optimizer (PSO) and tabu search (TS) algorithms.

Comparative or Homology Modeling

Molecular modeling and simulation of FabG, an enzyme involved in the fatty acid pathway of *Streptococcus pyogenes*

Rajamohmed Beema Shafreen, Shunmugiah Karutha Pandian [Alagappa University]

J. Mol.Graph. and Mod., **45,** 1–12, 2013.

A homology model of FabG was generated using the X-ray crystallographic structure of *Aquifex aeolicus* (PDB ID: 2PNF). The modeled structure was refined using energy minimization. Furthermore, active sites were predicted, and a large dataset of compounds was screened against SPFabG. The ligands were docked using the LigandFit module that is available from Discovery Studio version 2.5. From this list, 13 best hit ligands were chosen based on the docking score and binding energy.

A!

Comparative or Homology Modeling (Cont'd)

Modeling and molecular dynamics of the intrinsically disordered e7 proteins from high- and low-risk types of human papillomavirus

Nilson Nicolau-Junior, Silvana Giuliatti [University of São Paulo]

J. Mol.Mod., **19,** 4025-4037, 2013.

A!

Cervical cancer affects millions of women worldwide each year. Most cases of cervical cancer are caused by the sexually transmitted human papillomavirus (HPV). This is the first description of the modeling and molecular dynamics analysis of complete three-dimensional structures of high-risk (HPV types 16 and 18), low-risk (HPV type 11), and HPV type 01 E7 proteins. The models were constructed by a hybrid approach using homology (MODELLER) and ab initio (Rosetta) modeling, and the protein dynamics were simulated for 50 ns under normal pressure and temperature (NPT) conditions.

Homology modeling and structural comparison of leucine rich repeats of toll like receptors 1-10 of ruminants

Anandan Swathi, Gopal Dhinakar Raj, Angamuthu Raja, Krishnaswamy Gopalan Tirumurugaan[Tamil Nadu Veterinary and Animal Sciences University (TANUVAS)]

J. Mol.Mod., **19,** 3863-3874, 2013.

Toll-like receptors (TLRs) are transmembrane receptors composed of extra cellular leucine rich repeats (LRRs) that identify specific pathogen associated molecular patterns triggering a innate immune cascade. The LRR regions of TLR 1–10 proteins of goat (*Capra hircus*), sheep (*Ovis aries*), buffalo (*Bubalus bubalis*) and bovine (*Bos taurus*) were modeled using MODELLER 9v7 tool and validated. The similarities and variations of these 10 TLRs extracellular regions of each species were compared using online servers like FATCAT, SSM and SSAP.

Protein Sequence Analysis and Alignment

Capturing protein sequence–structure specificity using computational sequence design

Paul Mach, Patrice Koehl [University of California]

Proteins: Stru. Fun. & Bioinf., **81**, 1556–1570, 2013.

We explore this strategy on a large database of protein templates with 1747 members from different protein families. An automated method is used to design sequences for these templates. We use the backbones from the experimental structures as fixed templates, thread sequences on these backbones using a self-consistent mean field approach, and score the fitness of the corresponding models using a semi-empirical physical potential. Sequences designed for one template are translated into a hidden Markov model-based profile. We describe the implementation of this method, the optimization of its parameters, and its performance.

Protein Secondary structure

Infrared, Vibrational Circular Dichroism, and Raman Spectral Simulations for β-Sheet Structures with Various Isotopic Labels, Interstrand, and Stacking Arrangements Using Density Functional Theory

William R. W. Welch, Jan Kubelka[University of Wyoming], and Timothy A. Keiderling

J. Phys. Chem. B., **117**, 10343–10358, 2013**.**

Infrared (IR), Raman, and vibrational circular dichroism (VCD) spectral variations for different β-sheet structures were studied using simulations based on density functional theory (DFT) force field and intensity computations. The DFT vibrational parameters were obtained for β-sheet fragments containing nine-amides and constrained to a variety of conformations and strand arrangements. These were subsequently transferred onto corresponding larger β-sheet models, normally consisting of five strands with ten amides each, for spectral simulations. Further extension to fibril models composed of multiple stacked β-sheets was achieved by combining the transfer of DFT parameters for each sheet with dipole coupling methods for interactions between sheets.

Structural Analyses of Experimental ^{13}C Edited Amide I′ IR and VCD for Peptide β-Sheet Aggregates and Fibrils Using DFT-Based Spectral Simulations

William R. W. Welch, Timothy A. Keiderling[University of Illinois at Chicago], and Jan Kubelka

J. Phys. Chem. B., **117**, 10359–10369, 2013**.**

In this report, we simulate the IR and VCD spectra for models approximating structures of four β-sheet forming peptides previously experimentally studied using these methods with ^{13}C isotopic editing. Various register alignments are tested. Agreement with experiment is evaluated based on frequency shifts of both the ^{12}C and ^{13}C IR amide I′ signals, relative intensity patterns, and VCD spectra where available. While for the simulation of IR spectra canonical planar sheets provide a sufficient model system, for VCD simulation twisted, stacked sheets are required in order to reproduce strong couplet-like amide I′ VCD. Effects of the solvent (water) and amino acid side chains are also tested by using a simplified, electrostatic solvent model and atomic partial charges for the side chains.

Protein Confirmational Analysis

Conformational dynamics of full-length inducible human Hsp70 derived from microsecond molecular dynamics simulations in explicit solvent

Adrien Nicolaï, Patrice Delarue & Patrick Senet[UMR 6303 CNRS-Université de Bourgogne]

J. Biomol. Stru. and Dyn., **31**, 1111-1126, 2013.

Human 70 kDa heat shock protein (hHsp70) is an ATP-dependent chaperone and is currently an important target for developing new drugs in cancer therapy. Knowledge of the conformations of hHsp70 is central to understand the interactions between its nucleotide-binding domain (NBD) and substrate-binding domain (SBD) and is a prerequisite to design inhibitors. The conformations of ADP-bound (or nucleotide-free) hHsp70 and ATP-bound hHsp70 was investigated by using unbiased all-atom molecular dynamics (MD) simulations of homology models of hHsp70 in explicit solvent on a timescale of .5 and 2.7 μs, respectively.

Protein Confirmational Analysis (Cont'd)

Natural velvet antler polypeptide conformation prediction and molecular docking study with TGF-β1 complex

Yu-Dong Shang, Ji-Long Zhang, Qing-Chuan Zheng [Jilin University]

J. Mol.Mod., **19,** 3671-3682, 2013.

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Based on the chain A structures of hemoglobin (PDB code: 1HDS, 1IBE, 1FAW, 3AT5), the three dimensional (3D) structure of natural velvet antler polypeptide (nVAP) was constructed by homology modeling and molecular dynamics (MD) method. The structural rationality was further checked by Profile-3D and Procheck, both of which confirmed that the 3D structure of nVAP was reasonable. The modeled structure indicates that the stable conformation of nVAP is composed of two α-helixes.

Stereochemistry Rules: A Single Stereocenter Changes the Conformation of a Cyclic Tetrapeptide

Fee Li, Kenny Bravo-Rodriguez, Miguel Fernandez-Oliva, Juan M. Ramirez-Anguita, Klaus Merz, Manuela Winter, Christian W. Lehmann, Wolfram Sander[Max-Planck-Institut für Kohlenforschung], and Elsa Sanchez-Garcia

J. Phys. Chem. B., **117**, 10785–10791, 2013**.**

Two novel cyclo(Boc-Cys-Pro-Leu-Cys-OMe) peptides **1** and **2** containing the enantiomeric amino acids D-Leu and L-Leu, respectively, were synthesized to investigate the effect of chiral centers on peptide conformations. By combining a variety of experimental techniques (X-ray crystallography, 2D NMR spectroscopy, temperature-dependent ^{1}H NMR and IR spectroscopy, and UV-CD spectroscopy) with replica exchange molecular dynamics (REMD) techniques and quantum mechanics/molecular dynamics (QM/MM) calculations,

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Structural Properties of Non-Traditional Drug Targets Present New Challenges for Virtual Screening

Ragul Gowthaman, Eric J. Deeds, and John Karanicolas [University of Kansas]

J.Chem. Infor. and Mod. **53**, 2073–2081, 2013.

Traditional drug targets have historically included signaling proteins that respond to small molecules and enzymes that use small molecules as substrates. Increasing attention is now being directed toward other types of protein targets, in particular those that exert their function by interacting with nucleic acids or other proteins rather than small-molecule ligands. Here, we systematically compare existing examples of inhibitors of protein–protein interactions to inhibitors of traditional drug targets. While both sets of inhibitors bind with similar potency, we find that the inhibitors of protein–protein interactions typically bury a smaller fraction of their surface area upon binding to their protein targets.

A Contribution to the Drug Resistance Mechanism of Darunavir, Amprenavir, Indinavir, and Saquinavir Complexes with HIV-1 Protease Due to Flap Mutation I50V: A Systematic MM–PBSA and Thermodynamic Integration Study

Georgios Leonis, Thomas Steinbrecher, and Manthos G. Papadopoulos [National Hellenic Research Foundation]

J.Chem. Infor. and Mod. **53**, 2141–2153, 2013.

The emergence of HIV-1 drug-resistant mutations is the major problem against AIDS treatment. We employed MD calculations and free energy (MM–PBSA and thermodynamic integration) analyses on wild-type (WT) and mutated HIV-1 protease complexes with darunavir, amprenavir, indinavir, and saquinavir to clarify the mechanism of resistance due to the I50V flap mutation. Conformational analysis showed that the protease flaps are increasingly flexible in the I50V complexes. In the WT, stabilization of the HIV-1 PR structure is achieved via interflap and water-mediated hydrogen-bonding interactions between the flaps. Furthermore, hydrogen bonds between drugs and binding cavity residues (Asp29/29′/30/30′) are crucial for effective inhibition.

Protein Structure Analysis

Structure-based engineering of streptavidin monomer with a reduced biotin dissociation rate

Daniel DeMonte, Eric J. Drake, Kok Hong Lim, Andrew M. Gulick and Sheldon Park [University at Buffalo]

Proteins: Stru. Fun. & Bioinf., **81**, 1621–1633, 2013.

We recently reported the engineering of monomeric streptavidin, mSA, corresponding to one subunit of wild type (wt) streptavidin tetramer. The monomer was designed by homology modeling, in which the streptavidin and rhizavidin sequences were combined to engineer a high affinity binding pocket containing residues from a single subunit only. Although mSA is stable and binds biotin with nanomolar affinity, its fast off rate (k_{off}) creates practical challenges during applications. We obtained a 1.9 Å crystal structure of mSA bound to biotin to understand their interaction in detail, and used the structure to introduce targeted mutations to improve its binding kinetics.

Protein Dynamics

Characterizing a Histidine Switch Controlling pH-Dependent Conformational Changes of the Influenza Virus Hemagglutinin

Mohamad R. Kalani, Abdulvahab Moradi, Mahmoud Moradi, Emad Tajkhorshid [University of Illinois at Urbana-Champaign]

Biophysical Journal. **105**, 993-1003, 2013.

During the fusion of the influenza virus to the host cell, bending of the HA2 chain of hemagglutinin into a hairpin-shaped structure in a pH-dependent manner facilitates the fusion of the viral envelope and the endosomal membrane. To characterize the structural and dynamical responses of the hinge region of HA2 to pH changes and examine the role of a conserved histidine in this region (the hinge histidine), we have performed an extensive set of molecular dynamics (MD) simulations of 26-residue peptides encompassing the hinge regions of several hemagglutinin subtypes under both neutral and low pH conditions, modeled by the change of the protonation state of the hinge histidine.

Coupled Reversible and Irreversible Bistable Switches Underlying TGFβ-induced Epithelial to Mesenchymal Transition

Xiao-Jun Tian, Hang Zhang, Jianhua Xing [Virginia Tech]

Biophysical Journal. **105**, 1079-1089, 2013.

Epithelial to mesenchymal transition (EMT) plays an important role in embryonic development, tissue regeneration, and cancer metastasis. Whereas several feedback loops have been shown to regulate EMT, it remains elusive how they coordinately modulate EMT response to TGF-β treatment. We construct a mathematical model for the core regulatory network controlling TGF-β-induced EMT. Through deterministic analyses and stochastic simulations, we show that EMT is a sequential two-step program in which an epithelial cell first is converted to partial EMT then to the mesenchymal state, depending on the strength and duration of TGF-β stimulation.

Protein Dynamics (Cont'd)

Coarse-grained simulations of the salt dependence of the radius of gyration of polyelectrolytes as models for biomolecules in aqueous solution

F. Alarcón, G. Pérez-Hernández, E. Pérez, A. Gama Goicochea [Universidad Autónoma Metropolitana

Euro.biophy. jour., **42**, 661-672, 2013.

The salt dependent radius of gyration of a polyelectrolyte in aqueous solution is calculated in an environment where the polyelectrolyte is surrounded by a permeable membrane that exchanges only solvent particles with the bulk. We obtain additionally the scaling exponent of the gyration radius as a function of the polymerization degree, and find that the polyelectrolyte retains a stretched conformation during the condensation and re-expansion process, indicating that these effects are of an electrostatic nature.

Antifouling Glycocalyx-Mimetic Peptoids

Hyun Ok Ham, Sung Hyun Park, Josh W. Kurutz, Igal G. Szleifer, and Phillip B. Messersmith [Northwestern University]

J. Am. Chem. Soc., 2013, **135**, 13015–13022

The glycocalyx of the cell is composed of highly hydrated saccharidic groups conjugated to protein and lipid cores. Although components of the glycocalyx are important in cell–cell interactions and other specific biological recognition events, a fundamental role of the glycocalyx is the inhibition of nonspecific interactions at the cell surface. Inspired by glycoproteins present in the glycocalyx, we describe a new class of synthetic antifouling polymer composed of saccharide containing N-substituted polypeptide (glycopeptoid).

CHARMM36 all-atom additive protein force field: Validation based on comparison to NMR data

Jing Huang, Alexander D. MacKerell Jr [University of Maryland]

J. Comp. Chem., **34**, 2135–2145, 2013.

Protein structure and dynamics can be characterized on the atomistic level with both nuclear magnetic resonance (NMR) experiments and molecular dynamics (MD) simulations. Here, we quantify the ability of the recently presented CHARMM36 (C36) force field (FF) to reproduce various NMR observables using MD simulations. The studied NMR properties include backbone scalar couplings across hydrogen bonds, residual dipolar couplings (RDCs) and relaxation order parameter, as well as scalar couplings, RDCs, and order parameters for side-chain amino- and methyl-containing groups.

Molecular dynamics simulations of the thermal stability of tteRBP and ecRBP

Xian-li Feng, Xi Zhao[Jilin University], Hui Yu, Tie-dong Sun & Xu-ri Huang

J. Biomol. Stru. and Dyn., **31**, 1086-1100, 2013.

Molecular dynamics simulations were performed for investigating the thermal stability of the extremely thermophilic *Thermoanaerobacter tengcongensis* ribose binding protein (tteRBP) and the mesophilic homologous *Escherichia coli* ribose binding protein (ecRBP). The simulations for the two proteins were carried out under the room temperature (300 K) and the optimal activity temperature (tteRBP 375 K and ecRBP 329 K), respectively.

Protein Dynamics (Cont'd)

Molecular dynamics simulation to investigate the impact of disulfide bond formation on conformational stability of chicken cystatin I66Q mutant

Jianwei He, Linan Xu, Zhiyuan Zou, Nobuhiro Ueyama, Hui Li, Akio Kato, Gary W. Jones & YoutaoSong[LiaoningUniversity]

J. Biomol. Stru. and Dyn., **31**, 1101-1110, 2013.

Chicken cystatin (cC) mutant I66Q is located in the hydrophobic core of the protein and increases the propensity for amyloid formation. Here, we demonstrate that under physiological conditions, the replacement of Ile with the Gln in the I66Q mutant increases the susceptibility for the disulfide bond Cys71–Cys81 to be reduced when compared to the wild type (WT) cC. Molecular dynamics (MD) simulations under conditions favoring cC amyloid fibril formation are in agreement with the experimental results.

Insights into the drug resistance induced by the BaDHPS mutations: molecular dynamic simulations and MM/GBSA studies

Wen-Ting Chu, Ji-Long Zhang, Qing-Chuan Zheng **[**Jilin University**]**, Lin Chen, Qiao Xue & Hong-Xing Zhang

J. Biomol. Stru. and Dyn., **31**, 1127-1136, 2013.

Dihydropteroate synthase (DHPS) is essential for the folic acid biosynthetic pathway in prokaryotes; the mutation forms for DHPS are found to be relative to the urgent drug resistance problems. In our study, the *Bacillus anthracis* DHPS (BaDHPS) was selected for molecular dynamics and binding free energy studies to investigate the biochemistry behaviors of the wild-type and mutation form BaDHPS proteins (D184N and K220Q).

Effects of organic solvents and substrate binding on trypsin in acetonitrile and hexane media

Yanyan Meng, Yuan Yuan, Yanyan Zhu, Yanzhi Guo, Menglong Li, Zhimeng Wang, Xuemei Pu, Lin Jiang [Sichuan University]

J. Mol.Mod., **19,** 3749-3766, 2013.

In this work, we used molecular dynamic (MD) simulation to study trypsin with and without a six-amino-acid peptide bound in three different solvents (water, acetonitrile and hexane) in order to provide molecular information for well understanding the structure and function of enzymes in non-aqueous media. The results show that the enzyme is more compact and less native-like in hexane than in the other two polar solvents. The substrate could stabilize the native protein structure in the two polar media, but not in the non-polar hexane.

Equilibrium and folding simulations of NS4B H2 in pure water and water/2,2,2-trifluoroethanol mixed solvent: examination of solvation models

Man Guo, Ye Mei [East China Normal University

J. Mol.Mod., **19,** 3931-3939, 2013.

The structural stability and preference of a protein are highly sensitive to the environment accommodating it. In this work, the solvation effect on the structure and folding dynamics of a small peptide, NS4B H2, was studied by computer simulation. The native structure of NS4B H2 was solved previously in 50 % v/v water/2,2,2-trifluoroethanol (TFE) mixed solvent. In this work, both pure water and water/TFE cosolvent were utilized. The force field parameters for water were taken from the TIP3P water model, and those for TFE were generated following the routine of the general AMBER force field (GAFF).

Protein Dynamics (Cont'd)

High temperature unfolding of a truncated hemoglobin by molecular dynamics simulation

Ravi Datta Sharma [C.C.S. University], Rajnee Kanwal, Andrew M. Lynn, Prerna Singh, Syed Tazeen Pasha, Tasneem Fatma, Safdar Jawaid

J. Mol.Mod., **19,** 3993-4002, 2013.

Heme containing proteins are associated with peroxidase activity. The proteins like hemoglobin, myoglobins, cytochrome *c* and micro-peroxidase other than peroxidases have been shown to exhibit weak peroxidase-like activity. This weak peroxidase–like activity in hemoglobin-like molecules is due to heme moiety. We conducted molecular dynamics (MD) studies to decipher the unfolding path of Ba-Glb (a truncated hemoglobin from *Bacillus anthracis*) and the role of heme moiety to its unfolding path. The similar unfolding path is also observed in vitro by UV/VIS spectroscopy.

Computational Prediction of One-Electron Reduction Potentials and Acid Dissociation Constants for Guanine Oxidation Intermediates and Products

Brian T. Psciuk and H. Bernhard Schlegel [Wayne State University]

J. Phys. Chem. B., **117**, 9518–9531, 2013**.**

Reduction potentials and pK_a values were calculated for intermediates and products along three major pathways for guanine oxidation using the B3LYP and CBS-QB3 levels of theory with the SMD implicit solvation model. *N*-methylated nucleobases were used as models for nucleoside species. Ensemble averaged reduction potentials at pH 7 (E_7) were obtained by combining calculated standard reduction potentials with calculated pK_a values in addition to accounting for tautomerization energies. Calculated pK_a values are reasonable based on experimental estimates and chemical intuition.

Conformational Freedom in Tight Binding Enzymatic Transition-State Analogues

Matthew W. Motley, Vern L. Schramm, and Steven D. Schwartz [University of Arizona]

J. Phys. Chem. B., **117**, 9591-9597, 2013**.**

We conducted molecular dynamics simulations of both *Ec*MTAN and *Vc*MTAN in complex with BDIA to explore differences in protein dynamic architecture. Simulations revealed that electrostatic and hydrophobic interactions with BDIA are similar for both enzymes and thus unlikely to account for the difference in inhibitor affinity. The *Ec*MTAN–BDIA complex reveals a greater flexibility and conformational freedom of catalytically important atoms. We propose that conserved motions related to the *Ec*MTAN transition state correlate with the increased affinity of BDIA for *Ec*MTAN.

Insensitivity of Tryptophan Fluorescence to Local Charge Mutations

J. Nathan Scott and Patrik R. Callis [Montana State University]

J. Phys. Chem. B., **117**, 9598–9605, 2013**.**

The steady state fluorescence spectral maximum (λ_{max}) for tryptophan 140 of Staphylococcal nuclease remains virtually unchanged when nearby charged groups are removed by mutation, even though large electrostatic effects on λ_{max} might be expected. To help understand the underlying mechanism of this curious result, we have modeled λ_{max} with three sets of 50-ns molecular dynamics simulations in explicit water, equilibrated with excited state and with ground state charges.

Protein Dynamics (Cont'd)

Self-Assembly of Amphiphilic Peptide $(AF)_6H_5K_{15}$: Coarse-Grained Molecular Dynamics Simulation

Naresh Thota, Zhonglin Luo, Zhongqiao Hu, and Jianwen Jiang [National University of Singapore]

J. Phys. Chem. B., **117**, 9690–9698, 2013**.**

The assembly process and microscopic structures are analyzed in terms of the number of clusters, the radii of micelle, core and shell, and the density profiles of residues. A three-step process is proposed for the assembly: small clusters are initially aggregated and then merged into large clusters, eventually micelles are formed. The effects of simulation box size and peptide concentration are examined in detail. It is found that the micellar structures and microscopic properties are essentially independent of box size.

Helix Formation by Alanine-Based Peptides in Pure Water and Electrolyte Solutions: Insights from Molecular Dynamics Simulations

Filippos Ioannou, Epameinondas Leontidis, and Georgios Archontis [University of Cyprus]

J. Phys. Chem. B., **117**, 9866–9876, 2013**.**

Specific ion effects on oligopeptide conformations in solution are attracting strong research attention, because of their impact on the protein-folding problem and on several important biological–biotechnological applications. In this work, we have addressed specific effects of electrolytes on the tendency of oligopeptides toward formation and propagation of helical segments. We have used replica-exchange molecular dynamics (REMD) simulations to study the conformations of two short hydrophobic peptides [Ace-$(AAQAA)_3$-Nme (AQ), and Ace-A_8-Nme (A8)] in pure water and in aqueous solutions of sodium chloride (NaCl) and sodium iodide (NaI) with concentrations of 1 and 3 M.

Aβ(16–22) Peptides Can Assemble into Ordered β-Barrels and Bilayer β-Sheets, while Substitution of Phenylalanine 19 by Tryptophan Increases the Population of Disordered Aggregates

Luogang Xie, Yin Luo, and Guanghong Wei [Fudan University]

J. Phys. Chem. B., **117**, 10149–10160, 2013**.**

A recent experimental study reported that termini-uncapped Aβ(16–22) (with sequence KLVFFAE) peptides self-assembled into nanofibrils at pH 2.0. The oligomerization of this uncapped peptide at atomic level in acidic pH condition remains to be determined, as computational studies mainly focus on the self-assembly of capped Aβ(16–22) peptides at neutral pH condition. In this study, using replica exchange molecular dynamics (REMD) simulations with explicit solvent, we investigated the octameric structures of the uncapped Aβ(16–22) and its F19W variant at acidic pH condition. Our simulations reveal that the Aβ(16–22) octamers adopt various conformations, including closed β-barrels, bilayer β-sheets, and disordered aggregates.

Ab Initio Study of Molecular Interactions in Cellulose Iα

Ajitha Devarajan, Sergiy Markutsya, Monica H. Lamm, Xiaolin Cheng, Jeremy C. Smith, John Y. Baluyut, Yana Kholod, Mark S. Gordon, and Theresa L. Windus [Iowa State University]

J. Phys. Chem. B., **117**, 10430-10443, 2013**.**

The temperature dependence of methionine ligand dissociation and rebinding dynamics in cytochrome c in aqueous solution has been studied using classical molecular dynamics simulation. Results are compared with previous study of rebinding dynamics at 300 K in water in order to understand how the change of protein environment and the underlying protein energy landscape influence the dynamics. Rebinding dynamics at 77, 180, and 300 K exhibits changes in both time scale and mechanism as the protein and solvent undergo a dynamic "glass transition".

Protein Dynamics (Cont'd)

Structure and Dynamics of Uranyl(VI) and Plutonyl(VI) Cations in Ionic Liquid/Water Mixtures via Molecular Dynamics Simulations

Katie A. Maerzke, George S. Goff, Wolfgang H. Runde, William F. Schneider, and Edward J. Maginn [University of Notre Dame]

J. Phys. Chem. B., **117**, 10852–10868, 2013**.**

A fundamental understanding of the behavior of actinides in ionic liquids is required to develop advanced separation technologies. Spectroscopic measurements indicate a change in the coordination of uranyl in the hydrophobic ionic liquid 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([EMIM][Tf_2N]) as water is added to the system. Molecular dynamics simulations of dilute uranyl (UO_2^{2+}) and plutonyl (PuO_2^{2+}) solutions in [EMIM][Tf_2N]/water mixtures have been performed in order to examine the molecular-level coordination and dynamics of the actinyl cation (AnO_2^{2+}); An = U, Pu) as the amount of water in the system changes.

Substrate versus inhibitor dynamics of P-glycoprotein

Jerome Ma and Philip C. Biggin [University of Oxford]

Proteins: Stru. Fun. & Bioinf., **81**, 1653-1668, 2013.

We have performed MD simulations to examine the behaviour of P-gp. In agreement with previous reports, we found that P-gp undergoes large conformational changes which tended to result in the nucleotide-binding domains coming closer together. In all simulations, the approach of the NBDs was asymmetrical in agreement with previous observations for other ABC transporter proteins. To validate the simulations, we make extensive comparison to previous cross-linking data. Our results show very good agreement with the available data.

Free Energy Calculations

Following Easy Slope Paths on a Free Energy Landscape: The Case Study of the Trp-Cage Folding Mechanism

Fabrizio Marinelli [Max Planck Institute of Biophysics]

Biophysical Journal. **105**, 1236-1247, 2013.

In this work a new method for the automatic exploration and calculation of multidimensional free energy landscapes is proposed. The latter potential allows escaping a local free energy minimum following the direction of slow motions. This is different from metadynamics in which there is no specific direction of the biasing force and the computational effort increases significantly with the number of collective variables. The method is tested on the Ace-Ala_3-Nme peptide, and then it is applied to investigate the Trp-cage folding mechanism.

Ligand Binding/Docking

Computational gibberellin-binding channel discovery unraveling the unexpected perception mechanism of hormone signal by gibberellin receptor

Ge-Fei Hao, Sheng-Gang Yang, Guang-Fu Yang, Chang-Guo Zhan [University of Kentucky]

J. Comp. Chem., **34**, 2055–2064, 2013.

Gibberellins (GAs) are phytohormones essential for many developmental processes in plants. In this work, fundamental mechanism of hormone perception by receptor GID1 has been studied by performing computational simulations, revealing a new GA-binding channel of GID1 and a novel hormone perception mechanism involving only one conformational state of GID1. The novel hormone perception mechanism demonstrated here is remarkably different from the previously proposed/speculated mechanism [Murase et al., *Nature* **2008**,*456*, 459] involving two conformational states ("OPEN" and "CLOSED") of GID1.

Remarkable disparity in mechanical response among the extracellular domains of type I and II cadherins

Ruchuan Liu[National University of Singapore], Fei Wu & Jean Paul Thiery

J. Biomol. Stru. and Dyn., **31**, 1137-1149, 2013.

Cadherins, a large family of calcium-dependent adhesion molecules, are critical for intercellular adhesion. While crystallographic structures for several cadherins show clear structural similarities, their relevant adhesive strengths vary and their mechanisms of adhesion between types I and II cadherin subfamilies are still unclear. Here, stretching of cadherins was explored experimentally by atomic force microscopy and computationally by steered molecular dynamics (SMD) simulations, where partial unfolding of the E-cadherin ectodomains was observed.

Molecular basis for benzimidazole resistance from a novel β-tubulin binding site model

Rodrigo Aguayo-Ortiz , Oscar Méndez-Lucio , Antonio Romo-Mancillas , Rafael Castillo , Lilián Yépez-Mulia , José L. Medina-Franco , Alicia Hernández-Campos Universidad Nacional Autónoma de México (UNAM)]

J. Mol.Graph. and Mod., **45,** 26–37, 2013.

This study represents a first attempt towards understanding, at the molecular level, the structural composition of β-tubulin in all organisms, also suggesting possible resistance mechanisms. Furthermore, these results support the importance of benzimidazole derivative optimization in order to design more potent and selective (less toxic) molecules for the treatment of parasitic diseases.

Elucidating binding modes of zuonin A enantiomers to JNK1 via in silico methods

Daniel W. Dykstra , Kevin N. Dalby , Pengyu Ren [University of Texas at Austin]

J. Mol.Graph. and Mod., **45,** 38–44, 2013.

The results of this study provide new insight into potential binding modes for (−)-zuonin A and suggest that (−)-zuonin A interacts with JNK via an induced fit mechanism near the highly conserved φ_A-X-φ_B recognition site. Binding of (+)-zuonin A to JNK displays no such dynamic feature. The different binding modes may help explain differences in the inhibitory properties of the enantiomers although further experimental work would be necessary to fully confirm this interpretation

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Ligand Binding / Docking (Cont'd)

Experimental and Structural Testing Module to Analyze Paralogue-Specificity and Affinity in the Hsp90 Inhibitors Series

Tony Taldone [Memorial Sloan-Kettering Cancer Center], Pallav D. Patel, Maulik Patel, Hardik J. Patel, Christopher E. Evans, Anna Rodina, Stefan Ochiana, Smit K. Shah, Mohammad Uddin, Daniel Gewirth, and Gabriela Chiosis

J.Med.Chem., **56,** 6803–6818, 2013.

The assay can test rapidly and accurately the binding affinity of all major Hsp90 chemotypes and has a testing range that spans low nanomolar to millimolar binding affinities. We couple this assay with a computational analysis that allows for rationalization of paralogue selectivity and defines not only the major binding modes that relay pan-paralogue binding or, conversely, paralogue selectivity, but also identifies molecular characteristics that impart such features. The methods developed here provide a blueprint for parsing out the contribution of the four Hsp90 paralogues to the perceived biological activity with the current Hsp90 chemotypes and set the ground for the development of paralogue selective inhibitors.

Unbinding Pathways from the Glucocorticoid Receptor Shed Light on the Reduced Sensitivity of Glucocorticoid Ligands to a Naturally Occurring, Clinically Relevant Mutant Receptor

Anna Maria Capelli, Agostino Bruno, Antonio Entrena Guadix, and Gabriele Costantino [Largo F. Belloli]

J.Med.Chem., **56,** 7003–7014, 2013.

Herein, using steered MD simulations, we provide a detailed picture of the unbinding process of three clinically relevant GR modulators from GR ligand binding domains. The SMD protocol described here can be used to prioritize the synthesis of structural analogues on the basis of their potentials of mean force and calculated unbinding energies. Moreover, our results are instrumental in explaining at atomic resolution the weakened ability of dexamethasone to activate the naturally occurring mutant I747M GR, which is implicated in rare familial glucocorticoid resistance, clinically characterized by glucocorticoid insensitivity.

Simulations of Peptide-Graphene Interactions in Explicit Water

Aerial N. Camden, Stephen A. Barr, and Rajiv J. Berry [Air Force Research Laboratory]

J. Phys. Chem. B., **117**, 10691–10697, 2013**.**

The interaction of graphene with biomolecules has a variety of useful applications. In particular, graphitic surfaces decorated with peptides are being considered for high performance biochemical sensors. The interaction of peptides with graphene can also provide insight into the binding behavior of larger biomolecules. In this investigation, we have computed the binding enthalpies of a series of GXG tripeptides with graphene using classical molecular dynamics. Explicit water molecules were included to capture the effect of solvent. Of the twenty amino acid residues examined (X in GXG), arginine, glutamine, and asparagine exhibit the strongest interactions with graphene.

Cellular Retinaldehyde Binding Protein—Different Binding Modes and Micro-Solvation Patterns for High-Affinity 9-*cis*- and 11-*cis*-Retinal Substrates

Rachel E. Helbling, Christin S. Bolze, Marcin Golczak, Krzysztof Palczewski, Achim Stocker[University of Bern], and Michele Cascella

J. Phys. Chem. B., **117**, 10719–10729, 2013**.**

We use molecular dynamics (MD) simulations to determine the binding properties of different retinoid species to cellular retinaldehyde binding protein (CRALBP). The complexes formed by 9-*cis*-retinal or 11-*cis*-retinal bound to both the native protein and the R234W mutant, associated to Bothnia-retina dystrophy, are investigated. The presented studies are also complemented by analysis of the binding structures of the CRALBP/9-*cis*-retinol and CRALBP/9,13-*dicis*-retinal complexes.

Enzyme Catalysis

Insights into the Glycyl Radical Enzyme Active Site of Benzylsuccinate Synthase: A Computational Study

Vivek S. Bharadwaj, Anthony M. Dean, and C. Mark Maupin [Colorado School of Mines]

J. Am. Chem. Soc., 2013, **135**, 12279–12288

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The fumarate addition reaction, catalyzed by the enzyme benzylsuccinate synthase (BSS), is considered to be one of the most intriguing and energetically challenging reactions in biology. BSS belongs to the glycyl radical enzyme family and catalyzes the fumarate addition reaction, which enables microorganisms to utilize hydrocarbons as an energy source under anaerobic conditions. To enhance our molecular-level understanding of BSS, a computational approach involving homology modeling, docking studies, and molecular dynamics (MD) simulations has been used to deduce the structure of BSS's catalytic subunit (BSSα) and illuminate the molecular basis for the fumarate addition reaction.

Mycobacterium tuberculosis Shikimate Kinase Inhibitors: Design and Simulation Studies of the Catalytic Turnover

Beatriz Blanco, Verónica Prado, Emilio Lence, José M. Otero, Carmela Garcia-Doval, Mark J. van Raaij, Antonio L. Llamas-Saiz, Heather Lamb, Alastair R. Hawkins, and Concepción González-Bello [Universidad de Santiago de Compostela]

J. Am. Chem. Soc., 2013, **135**, 12366–12376

Shikimate kinase (SK) is an essential enzyme in several pathogenic bacteria and does not have any counterpart in human cells, thus making it an attractive target for the development of new antibiotics. The key interactions of the substrate and product binding and the enzyme movements that are essential for catalytic turnover of the *Mycobacterium tuberculosis* shikimate kinase enzyme (*Mt*-SK) have been investigated by structural and computational studies. Based on these studies several substrate analogs were designed and assayed.

Insight into TPMT*23 mutation mis-folding using molecular dynamics simulation and protein structure analysis

Sofiene Larif [Metabolic Biophysics and Applied Pharmacology Laboratory], Chaker Ben Salem,ZohraSoua, HoussemHmouda & Kamel Bouraoui

J. Biomol. Stru. and Dyn., **31**, 1066-1076, 2013.

Thiopurine S-methyltransferase (TPMT) is an important enzyme that metabolizes thiopurine drugs. This enzyme exhibits a large number of interindividual polymorphism. TPMT*23 polymorphism has been reported in a few cases in the world in co-dominance with TPMT*3A. The phenotype has been reported to affect enzyme activity in vivo and in vitro. Its underlying structural basis is not clarified yet. In our study, the wild type (WT) protein structure was analyzed and the amino acids bordering water channels in thiopurine sites were identified.

Construction and assessment of reaction models between F1F0-synthase and organotin compounds: molecular docking and quantum calculations

Marcus V.J. Rocha, Teodorico C. Ramalho [Federal University of Lavras, Melissa S. Caetano & Elaine F.F. da Cunha

J. Biomol. Stru. and Dyn., **31**, 1175-1181, 2013.

Organotin compounds are the active components of some fungicides, which are potential inhibitors of the F_1F_0-ATP synthase. The studies about the reaction mechanism might indicate a pathway to understand how these compounds work in biological systems, however, has not been clarified so far. In this line, molecular modeling studies and density functional theory calculations were performed in order to understand the molecular behavior of those compounds when they interact with the active site of the enzyme.

Enzyme Catalysis (Cont'd)

Theoretical studies on the binding of rhenium(I) complexes to inducible nitric oxide synthase

Bruno L. Oliveira [Universidade Técnica de Lisboa] , Irina S. Moreira , Pedro A. Fernandes , Maria J. Ramos , Isabel Santos , João D.G. Correia ,

J. Mol.Graph. and Mod., **45,** 13–25, 2013.

Considering our interest in the design of innovative radiometal-based complexes for *in vivo* imaging of nitric oxide synthase (NOS), we have recently introduced a set of $M(CO)_3$-complexes (M = ^{99m}Tc, Re) containing a pendant N^{ω}-NO_2-L-arginine moiety, a known inhibitor of the enzyme. Enzymatic assays with purified inducible NOS have shown that the non-radioactive surrogates with 3-(**Re1**; K_i = 84 μM) or 6-carbon linkers (**Re2**; K_i = 6 μM) are stronger inhibitors than the respective metal-free conjugates **L1** (K_i = 178 μM) and **L2**(K_i = 36 μM), with **Re2** displaying the highest inhibitory potency.

Insights into the structure–function relationship of disease resistance protein HCTR in maize (*Zea mays* L.): A computational structural biology approach

Budheswar Dehury , Mousumi Sahu , Mahesh Chandra Patra , Kishore Sarma , Jagajjit Sahu ,Priyabrata Sen , Mahendra Kumar Modi , Manabendra Dutta Choudhury , Madhumita Barooah [Assam Agricultural University]

J. Mol.Graph. and Mod., **45,** 50–64, 2013.

The disease resistance gene *Hm*1 of maize encodes a NADPH-dependent reductase enzyme, HC-toxin reductase (HCTR) that detoxifies the HC toxin secreted by the race specific fungus *Cochliobolus carbonum*race 1. HCTR enzyme shares 29.6% sequence identity with dihydroflavonol reductase (DFR) of grape, a key enzyme involved in flavonoid biosynthesis. Here we report the comparative modelling, molecular dynamics simulation and docking studies to explain the structure–function relationship and the mode of cofactor (NADPH) binding in HCTR enzyme at the molecular level. The nucleotide binding domain of modelled HCTR adopts a classic Rossmann fold and possesses a consensus glycine rich GxGxxG motif.

Concerted Proton Transfer Mechanism of *Clostridium thermocellum* Ribose-5-phosphate Isomerase

Jun Wang and Weitao Yang [Duke University, Durham]

J. Phys. Chem. B., **117**, 9354–9361, 2013**.**

Clostridium thermocellum ribose-5-phosphate isomerase (CtRpi), belonging to the RpiB family, has recently been employed in the industrial production of rare sugars because of its fast reaction kinetics and narrow substrate specificity. We have performed quantum mechanical/molecular mechanical simulations of this rate-limiting step of the reaction catalyzed by CtRpi with the substrate D-ribose. Our results demonstrate that the deprotonated Cys65 is not a stable reactant. Instead, our calculations revealed a concerted proton-transfer mechanism:

Combined QM/MM Investigation on the Light-Driven Electron-Induced Repair of the (6–4) Thymine Dimer Catalyzed by DNA Photolyase

Shirin Faraji[University of Jyväskylä], Gerrit Groenhof, and Andreas Dreuw

J. Phys. Chem. B., **117**, 10071–10079, 2013**.**

The (6–4) photolyases are blue-light-activated enzymes that selectively bind to DNA and initiate splitting of mutagenic thymine (6–4) thymine photoproducts (T(6–4)T-PP) via photoinduced electron transfer from flavin adenine dinucleotide anion ($FADH^-$) to the lesion triggering repair. In the present work, the repair mechanism after the initial electron transfer and the effect of the protein/DNA environment are investigated theoretically by means of hybrid quantum mechanical/molecular mechanical (QM/MM) simulations using X-ray structure of the enzyme–DNA complex.

Enzyme Catalysis (Cont'd)

Catalytic Mechanism of Hyaluronate Lyase from *Spectrococcus pneumonia*: Quantum Mechanical/Molecular Mechanical and Density Functional Theory Studies

Min Zheng and Dingguo Xu [Sichuan University]

J. Phys. Chem. B., **117**, 10161–10172, 2013**.**

Hyaluronate lyase from *Spectrococcus pneumonia* can degrade hyaluronic acid, which is one of the major components in the extracellular matrix. The major functions of hyaluronan are to regulate water balance and osmotic pressure and act as an ion-exchange resin. It has been suggested in our previous molecular dynamics simulation that the binding of the substrate molecule could lead to the ionization of Y408 and protonation of H399. Followed by our recent molecular dynamics simulation of the enzyme–substrate complex, a unified proton abstraction and donation mechanism for this enzyme can be established using a combined quantum mechanical and molecular mechanical approach and density functional theory method.

Charge Transfer in E. coli DNA Photolyase: Understanding Polarization and Stabilization Effects via QM/MM Simulations

Gesa Lüdemann, P. Benjamin Woiczikowski, Tomáš Kubař, Marcus Elstner, and Thomas B. Steinbrecher[Karlsruhe Institute for Technology]

J. Phys. Chem. B., **117**, 10769–10778, 2013**.**

We study fast hole transfer events in *E. coli* DNA photolyase, a key step in the photoactivation process, using a multiscale computational method that combines nonadiabatic propagation schemes and linear-scaling quantum chemical methods with molecular mechanics force fields. This scheme allows us to follow the time-dependent evolution of the electron hole in an unbiased fashion; that is, no assumptions about hole wave function localization, time scale separation, or adiabaticity of the process have to be made beforehand.

Protein-Protein Interactions

Effect of mutation at the interface of Trp-repressor dimeric protein: a steered molecular dynamics simulation

German Miño [Universidad de Chile], Mauricio Baez, Gonzalo Gutierrez

Euro.biophy. jour., **42**, 683-690, 2013.

Experimentally, changes in the interface are evaluated by generating specific mutations at one or more points of the protein structure. Here, such an evaluation is performed by means of steered molecular dynamics and use of a dimeric model of tryptophan repressor and in-silico mutants as a test case. Analysis of four particular cases shows that, in principle, it is possible to distinguish between wild-type and mutant forms by examination of the total energy and force–extension profiles.

Protein-Protein interactions (Cont'd)

An information-theoretic classification of amino acids for the assessment of interfaces in protein–protein docking

Christophe Jardin, Arno G. Stefani, Martin Eberhardt, Johannes B. Huber, Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J. Mol.Mod., **19,** 3901-3910, 2013.

Docking represents a versatile and powerful method to predict the geometry of protein–protein complexes. However, despite significant methodical advances, the identification of good docking solutions among a large number of false solutions still remains a difficult task. We have previously demonstrated that the formalism of mutual information (MI) from information theory can be adapted to protein docking, and we have now extended this approach to enhance its robustness and applicability. A large dataset consisting of 22,934 docking decoys derived from 203 different protein–protein complexes was used for an MI-based optimization of reduced amino acid alphabets representing the protein–protein interfaces.

Identification of efflux proteins using efficient radial basis function networks with position-specific scoring matrices and biochemical properties

Yu-Yen Ou[Yuan Ze University], Shu-An Chen, Yun-Min Chang, Devadasan Velmurugan, Kazuhiko Fukui and M. Michael Gromiha

Proteins: Stru. Fun. & Bioinf., **81**, 1634–1643, 2013.

In this work, we have developed a method based on radial basis function networks using position specific scoring matrices (PSSM) and amino acid properties. We noticed that the C-terminal domain of efflux proteins contain vital information for discrimination. Our method showed an accuracy of 78 and 92% in discriminating efflux proteins from transporters and membrane proteins, respectively using fivefold cross-validation. We utilized our method for annotating the genomes*E. coli* and *P. aeruginosa* and it predicted 8.7 and 9.2% of proteins as efflux proteins in these genomes, respectively.

Membrane Proteins and Lipid Peptide Interactions

Dodecyl Maltoside Protects Membrane Proteins In Vacuo

Sarah L. Rouse, Julien Marcoux, Carol V. Robinson, Mark S.P. Sansom [University of Oxford]

Biophysical Journal. **105**, 648-656, 2013.

We compared two membrane protein architectures (an α-helical bundle versus a β-barrel) and two different detergent types (phosphocholines versus an alkyl sugar) with respect to protein stability and detergent packing. The β-barrel membrane protein remained stable as a protein-detergent complex in vacuum. Zwitterionic detergents formed conformationally destabilizing interactions with an α-helical membrane protein after detergent micelle inversion driven by dehydration in vacuum.

Interaction of the Complexin Accessory Helix with the C-Terminus of the SNARE Complex: Molecular-Dynamics Model of the Fusion Clamp

Maria Bykhovskaia [Universidad Central del Caribe], Anand Jagota, Agustin Gonzalez, Alexander Vasin, J. Troy Littleton

Biophysical Journal. **105**, 679-690, 2013.

To test this model, we performed experimental and computational characterizations of the *syx3-69Drosophila* mutant, which has a point mutation in syntaxin that causes increased spontaneous fusion. We found that this mutation disrupts the interaction of the Cpx AH with synaptobrevin, partially imitating the *cpx* null phenotype. Our results support a model in which the Cpx AH clamps fusion by binding to the synaptobrevin C-terminus, thus preventing full SNARE zippering.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

NMR-Based Simulation Studies of Pf1 Coat Protein in Explicit Membranes

Xi Cheng, Sunhwan Jo, Francesca M. Marassi, Wonpil Im [The University of Kansas]

Biophysical Journal. **105**, 691-698, 2013.

We have performed NMR-restrained molecular dynamics simulations to refine the structure of the membrane-bound form of Pf1 coat protein in explicit lipid bilayers using the recently measured chemical shift anisotropy, dipolar coupling, and residual dipolar coupling data. From the simulations, we have characterized detailed protein-lipid interactions and explored the dynamics. All simulations are stable and the NMR restraints are well satisfied.

In silico modeling and experimental evidence of coagulant protein interaction with precursors for nanoparticle functionalization

Chuka Okoli [Royal Institute of Technology (KTH)], Selvaraj Sengottaiyan, N. Arul Murugan, Asalapuram R. Pavankumar, Hans Ågren & Gunaratna Kuttuva Rajarao

J. Biomol. Stru. and Dyn., **31**, 1182-1190, 2013.

The design of novel protein–nanoparticle hybrid systems has applications in many fields of science ranging from biomedicine, catalysis, water treatment, etc. The main barrier in devising such tool is lack of adequate information or poor understanding of protein–ligand chemistry. Here, we establish a new strategy based on computational modeling for protein and precursor linkers that can decorate the nanoparticles. *Moringa oleifera* ($MO_{2.1}$) seed protein that has coagulation and antimicrobial properties was used.

Effects of protein binding on a lipid bilayer containing local anesthetic articaine, and the potential of mean force calculation: a molecular dynamics simulation approach

Sepideh Amjad-Iranagh, Abbas Yousefpour, Parto Haghighi, Hamid Modarress [Amirkabir University of Technology]

J. Mol.Mod., **19,** 3831-3842, 2013.

Articaine, as a local anesthetic drug has been simulated in neutral and charged forms, and its interaction with the dimyristoylphosphatidylcholine (DMPC) lipid bilayer membrane is investigated by molecular dynamics simulation using GROMACS software. In order to obtain the optimum location of the drug molecules, as they penetrate into the membrane, umbrella sampling is applied and the free energy is calculated. The effect of protein binding to DMPC membrane on the process of drug diffusion through the membrane is considered.

Biomolecular Simulations with the Transferable Potentials for Phase Equilibria: Extension to Phospholipids

Navendu Bhatnagar, Ganesh Kamath, and Jeffrey J. Potoff [Wayne State University]

J. Phys. Chem. B., **117**, 9910–9921, 2013**.**

The temperature dependence of methionine ligand dissociation and rebinding dynamics in cytochrome c in aqueous solution has been studied using classical molecular dynamics simulation. Results are compared with previous study of rebinding dynamics at 300 K in water in order to understand how the change of protein environment and the underlying protein energy landscape influence the dynamics. Rebinding dynamics at 77, 180, and 300 K exhibits changes in both time scale and mechanism as the protein and solvent undergo a dynamic "glass transition".

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Contributions of water transfer energy to protein-ligand association and dissociation barriers: Watermap analysis of a series of p38α MAP kinase inhibitors

Robert A. Pearlstein [Novartis Institutes for BioMedical Research] ,Woody Sherman,Robert Abel

Proteins: Stru. Fun. & Bioinf., **81**, 1509–1526, 2013.

In the present work, we test this hypothesis on another kinetically-determined protein-ligand system—that of p38α and eight Type II BIRB 796 inhibitor analogs.
We calculated the solvation properties of the DFG-out protein conformation using an explicit solvent molecular dynamics simulation and thermodynamic analysis method implemented in WaterMap to predict the enthalpic and entropic costs of water transfer to and from bulk solvent incurred upon association and dissociation of each inhibitor.

S!

Protein Folding

Right- and left-handed three-helix proteins. I. Experimental and simulation analysis of differences in folding and structure

Anna V. Glyakina,Leonid B. Pereyaslavets, Oxana V. Galzitskaya[Russian Academy of Sciences]

Proteins: Stru. Fun. & Bioinf., **81**, 1527–1541, 2013.

The studies allowed us to determine the orders of folding of the secondary-structure elements in these domains and amino acid residues which are important for the folding. The obtained data are in good correlation with each other and with the experimental data. Structural analysis of these proteins demonstrated that the left-handed domains have a lesser number of contacts per residue and a smaller radius of cross section than the right-handed domains. This may be one of the explanations of the observed fact.

The stability of cylindrin β-barrel amyloid oligomer models—A molecular dynamics study

Workalemahu M. Berhanu, Ulrich H. E. Hansmann [University of Oklahoma]

Proteins: Stru. Fun. & Bioinf., **81**, 1542–1555, 2013.

In the present article we investigate the effect of mutations in the hydrophobic cores on the structure and dynamic of the β-barrels using all atom multiple molecular dynamics simulations with an explicit solvent. Extending previous experiments with molecular dynamics simulations we systematically test how stability and formation of cylindrin depends on the interplay between hydrophobicity and steric effects of the core residues.

***Ab initio* folding of extended α-helix: A theoretical study about the role of electrostatic polarization in the folding of helical structures**

Raudah Lazim, Caiyi Wei, Tiedong Sun and Dawei Zhang [Nanyang Technological University]

Proteins: Stru. Fun. & Bioinf., **81**, 1610–1620, 2013.

In this study, 2khk will be used as a benchmark case serving as a means to compare the ability of polarized (AHBC) and nonpolarized force field in the folding of an extended helix. Analyses conducted revealed the ability of the AHBC scheme in effectively folding the extended helix by promoting helix growth through the stabilization of backbone hydrogen bonds upon formation during the folding process. Similar observations were also noted when AHBC scheme was employed during the folding of C34 and N36.

Protein-Nucleic acid Interactions

Urea-Induced Denaturation of $PreQ_1$-Riboswitch

Jeseong Yoon, D. Thirumalai, and Changbong Hyeon [Korea Institute for Advanced Study]

J. Am. Chem. Soc., 2013, **135**, 12112–12121

Our simulations reveal that the denaturation of RNA structures is mainly driven by the hydrogen-bonding and stacking interactions of urea with the bases. Through detailed studies of the simulation trajectories, we found that geminate pairs between urea and bases due to hydrogen bonds and stacks persist only ~0.1–1 ns, which suggests that the urea–base interaction is highly dynamic. Most importantly, the early stage of base-pair disruption is triggered by penetration of water molecules into the hydrophobic domain between the RNA bases.

A method for in silico identification of SNAIL/SLUG DNA binding potentials to the E-box sequence using molecular dynamics and evolutionary conserved amino acids

Jeremy W. Prokop [The University of Akron], Yuanjie Liu, Amy Milsted, Hongzhuang Peng, Frank J. Rauscher III

J. Mol.Mod., **19,** 3463-3469, 2013.

Binding of transcription factors to DNA is a dynamic process allowing for spatial- and sequence-specificity. Many methods for determination of DNA–protein structures do not allow for identification of dynamics of the search process, but provide only a single snapshot of the most stable binding. In order to better understand the dynamics of DNA binding as a protein encounters its cognate site, we have created a computer-based DNA scanning array macro that sequentially inserts a high affinity DNA consensus binding site at all possible locations in a predicted protein–DNA interface.

An Extended Pyrrolobenzodiazepine–Polyamide Conjugate with Selectivity for a DNA Sequence Containing the ICB2 Transcription Factor Binding Site

Federico Brucoli, Rachel M. Hawkins, Colin H. James, Paul J. M. Jackson, Geoff Wells, Terence C. Jenkins, Tom Ellis, Minal Kotecha, Daniel Hochhauser, John A. Hartley, Philip W. Howard, and David E. Thurston [King's College London]

J.Med.Chem., **56,** 6339–6351, 2013.

The binding of nuclear factor Y (NF-Y) to inverted CCAAT boxes (ICBs) within the promoter region of DNA topoisomerase IIα results in control of cell differentiation and cell cycle progression. Thus, NF-Y inhibitory small molecules could be employed to inhibit the replication of cancer cells. A library of pyrrolobenzodiazepine (PBD) C8-conjugates consisting of one PBD unit attached to tri-heterocyclic polyamide fragments was designed and synthesized. The DNA-binding affinity and sequence selectivity of each compound were evaluated in DNA thermal denaturation and DNase I footprinting assays, and the ability to inhibit binding of NF-Y to ICB1 and ICB2 was studied using an electrophoretic mobility shift assay (EMSA).

A Dynamic G-Quadruplex Region Regulates the HIV-1 Long Terminal Repeat Promoter

Rosalba Perrone, Matteo Nadai, Ilaria Frasson, Jerrod A. Poe, Elena Butovskaya, Thomas E. Smithgall, Manlio Palumbo, Giorgio Palù, and Sara N. Richter [University of Padua]

J.Med.Chem., **56,** 6521–6530, 2013.

Here we show that also the HIV-1 LTR promoter exploits G-quadruplex-mediated transcriptional regulation with striking similarities to eukaryotic promoters and that treatment with a G-quadruplex ligand inhibits HIV-1 infectivity. Computational analysis on 953 HIV-1 strains substantiated a highly conserved G-rich sequence corresponding to Sp1 and NF-κB binding sites. Biophysical/biochemical analysis proved that two mutually exclusive parallel-like intramolecular G-quadruplexes, stabilized by small molecule ligands, primarily fold in this region.

Protein-Nucleic Acid Interactions (Cont'd)

In Silico Studies toward Understanding the Interactions of DNA Base Pairs with Protonated Linear/Cyclic Diamines

Anik Sen, Debashis Sahu, and Bishwajit Ganguly [CSIR-Central Salt and Marine Chemicals Research Institute]

J. Phys. Chem. B., **117**, 9840–9850, 2013**.**

In search of efficient polyamine analogues, we have performed DFT calculations on the interactions of some simple cyclic and constrained protonated diamines with the DNA base pairs and compared the results with those obtained for the corresponding interactions involving linear diamines, which mimic biogenic polyamines such as spermine. The interactions are mainly governed by the strong hydrogen bonding between the ligand and the DNA base pairs. The DFT calculations suggest that the major-groove N7 interaction (GC base pair) with linear diamine is energetically more favored than other possible interactions, as reported with spermine.

Significant Strength of Charged DNA–Protein π–π Interactions: A Preliminary Study of Cytosine

Rachael A. Wells, Jennifer L. Kellie, and Stacey D. Wetmore [University of Lethbridge]

J. Phys. Chem. B., **117**, 10462–10474, 2013**.**

Through comparison to previous literature on the π–π interactions between the DNA nucleobases and the aromatic amino acid residues, this work will allow for comparisons between DNA–protein interactions involving aromatic and acyclic R-side chains, as well as comparisons of the relative geometric dependence and magnitude of π–π (C:DE), π_{cation}–π (C:R^+), and π_{anion}–π (C:DE^-) interactions

Nucleic Acids

A Novel Implicit Solvent Model for Simulating the Molecular Dynamics of RNA

Yufeng Liu, Esmael Haddadian, Tobin R. Sosnick, Karl F. Freed, Haipeng Gong [Tsinghua University]

Biophysical Journal. **104**, 1248-1257, 2013.

We present a novel, to our knowledge, implicit solvent model for simulating nucleic acids by combining the Langevin–Debye model and the Poisson–Boltzmann equation to provide a better estimate of the electrostatic screening of both the water and counter ions. Tests of the model involve comparisons of implicit and explicit solvent simulations for three RNA targets with 20, 29, and 75 nucleotides.

Structural model of the complete poly(A) region of HIV-1 pre-mRNA

Rajesh Singh & M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Biomol. Stru. and Dyn., **31**, 1044-1056, 2013.

In the HIV-1 retrovirus, identical sequences encompassing the AAUAAA hexamer and the U/GU-rich downstream sequence element (DSE) that compose the core poly(A) site are present at both the 5′ and 3′ ends of the HIV-1 pre-mRNA. The AAUAAA hexamer is partly occluded by base pairing in the upper part of a semi-stable polyA hairpin. This sets the stage for regulation of HIV-1 polyadenylation, which involves reaction suppression at the 5′ end and its stimulation at the 3′ end. Efficient utilization of the 3′ core poly(A) site is promoted by major and minor upstream sequence elements (USEs) which are uniquely present at the 3′ end of the HIV-1 transcript.

Nucleic Acids (Cont'd)

In silico discrimination of nsSNPs in*hTERT* gene by means of local DNA sequence context and regularity

C. George Priya Doss [VIT University], Chiranjib Chakraborty, B. Rajith, N. Nagasundaram

J. Mol.Mod., **19,** 3517-3527, 2013.

Understanding and predicting the significance of novel genetic variants revealed by DNA sequencing is a major challenge to integrate and interpret in medical genetics with medical practice. Recent studies have afforded significant advances in characterization and predicting the association of single nucleotide polymorphisms in human *TERT* with various disorders, but the results remain inconclusive. In this context, a comparative study between disease causing and novel mutations in*hTERT* gene was performed computationally.

Theoretical study of the pre- and post-translational effects of adenine and thymine tautomers and methyl derivatives

Noel Gardner, David Magers, Glake Hill Jr. [Jackson State University]

J. Mol.Mod., **19,** 3543-3549, 2013.

The study of pre-translational effects (ionization, tautomerization) and post-translational effects (methylation) of adenine and thymine has only recently been the focus of some studies. These effects can potentially help regulate gene expression as well as potentially disrupt normal gene function. Because of this wide array of roles, greater insight into these effects in deoxyribonucleic acids (DNA) are paramount. In this work, we attempt to shed light upon the pre-translational effects and post translational effects of adenine and thymine by investigating the electron affinities (EAs) and ionization potentials (IPs) of the major and minor tautomers and their methyl derivatives.

Surfaces, Catalysts, and Materials Subjects

Calculations of Critical Micelle Concentration by Dissipative Particle Dynamics Simulations: The Role of Chain Rigidity

Ming-Tsung Lee, Aleksey Vishnyakov, and Alexander V. Neimark [The State University of New Jersey]

J. Phys. Chem. B., **117**, 10304–10310, 2013**.**

Micelle formation in surfactant solutions is a self-assembly process governed by complex interplay of solvent-mediated interactions between hydrophilic and hydrophobic groups, which are commonly called heads and tails. However, the head–tail repulsion is not the only factor affecting the micelle formation. For the first time, we present a systematic study of the effect of chain rigidity on critical micelle concentration and micelle size, which is performed with the dissipative particle dynamics simulation method.

2. METHODOLOGY

Quantitative Structure-Activity Relations

QSARINS: A new software for the development, analysis, and validation of QSAR MLR models

Paola Gramatica [University of Insubria], Nicola Chirico, Ester Papa, Stefano Cassani, Simona Kovarich

J. Comp. Chem., **34**, 2121–2132, 2013.

QSARINS (QSAR-INSUBRIA) is a new software for the development and validation of multiple linear regression Quantitative Structure-Activity Relationship (QSAR) models by Ordinary Least Squares method and Genetic Algorithm for variable selection. This program is mainly focused on the external validation of QSAR models. Various tools for explorative analysis of the datasets by Principal Component Analysis, prereduction of input molecular descriptors, splitting of datasets in training and prediction sets, detection of outliers and interpolated or extrapolated predictions, internal and external validation by different parameters, consensus modeling and various plots for visualizations are implemented.

Synthesis and Quantitative Structure–Activity Relationship of Imidazotetrazine Prodrugs with Activity Independent of *O*6-Methylguanine-DNA-methyltransferase, DNA Mismatch Repair, and p53

Dimitrios Pletsas, Elrashied A. E. Garelnabi, Li Li, Roger M. Phillips, and Richard T. Wheelhouse [University of Bradford]

J.Med.Chem., **56,** 7120–7132, 2013.

The antitumor prodrug temozolomide is compromised by its dependence for activity on DNA mismatch repair (MMR) and the repair of the chemosensitive DNA lesion, *O*6-methylguanine (*O*6-MeG), by *O*6-methylguanine-DNA-methyltransferase (E.C. 2.1.1.63, MGMT). This is achieved through a switch of mechanism so that bioactivity derives from imidazotetrazine-generated arylaziridinium ions that principally modify guanine-*N*7 sites on DNA. Mono- and bifunctional analogues are reported, and a quantitative structure–activity relationship (QSAR) study identified the *p*-tolyl-substituted bifunctional congener as optimized for potency, MGMT-independence, and MMR-independence.

Localized Heuristic Inverse Quantitative Structure Activity Relationship with Bulk Descriptors Using Numerical Gradients

Jonna Stålring [AstraZeneca R&D], Pedro R. Almeida, Lars Carlsson, Ernst Helgee Ahlberg, Catrin Hasselgren, and Scott Boyer

J.Chem. Infor. and Mod. **53**, 2001–2017, 2013.

This paper introduces localized heuristic inverse QSAR, which provides an assessment of the relative ability of the descriptors to influence the biological response in an area localized around the predicted compound. The method is based on numerical gradients with parameters optimized using data sets sampled from analytical functions. The heuristic character of the method reduces the computational requirements and makes it applicable not only to fragment based methods but also to QSARs based on bulk descriptors.

Molecular Dynamics

A Computational Model of Reactive Oxygen Species and Redox Balance in Cardiac Mitochondria

Laura D. Gauthier [Johns Hopkins University School of Medicine], Joseph L. Greenstein, Sonia Cortassa, Brian O'Rourke, Raimond L. Winslow

Biophysical Journal. **105**, 1045-1056, 2013.

Elevated levels of reactive oxygen species (ROS) play a critical role in cardiac myocyte signaling in both healthy and diseased cells. In the presence of ample ROS scavenging, total ROS production is moderate in state 3 and increases substantially under state 4 conditions. The ROS production model was extended by combining it with a minimal model of ROS scavenging. When the mitochondrial redox status was oxidized by increasing the proton permeability of the inner mitochondrial membrane, simulations with the combined model show that ROS levels initially decline as production drops off with decreasing $\Delta\Psi_m$ and then increase as scavenging capacity is exhausted.

Cell Optical Density and Molecular Composition Revealed by Simultaneous Multimodal Label-Free Imaging

Nicolas Pavillon, Alison J. Hobro, Nicholas I. Smith [Osaka University]

Biophysical Journal. **105**, 1123-1132, 2013.

We show how Raman imaging can be combined with independent but simultaneous phase measurements of unlabeled cells, with the resulting data providing information on how the light is retarded and/or scattered by molecules in the cell. We then show, for the first time to our knowledge, how the chemistry of the cell highlighted in the Raman information is related to the cell quantitative phase information revealed in digital holographic microscopy by quantifying how the two sets of spatial information are correlated.

Random Walk on a Leash: A Simple Single-Molecule Diffusion Model for Surface-Tethered Redox Molecules with Flexible Linkers

Kuan-Chun Huang and Ryan J. White [University of Maryland, Baltimore County]

J. Am. Chem. Soc., 2013, **135**, 12808–12817

We develop a random walk model to simulate the Brownian motion and the electrochemical response of a single molecule confined to an electrode surface via a flexible molecular tether. We use our simple model, which requires no prior knowledge of the physics of the molecular tether, to predict and better understand the voltammetric response of surface-confined redox molecules when motion of the redox molecule becomes important. The single molecule is confined to a hemispherical volume with a maximum radius determined by the flexible molecular tether (5–20 nm) and is allowed to undergo true three-dimensional diffusion.

QM and QM/MM

Amine Oxidation Mediated by Lysine-Specific Demethylase 1: Quantum Mechanics/Molecular Mechanics Insights into Mechanism and Role of Lysine 661

Bora Karasulu, Mahendra Patil, and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Am. Chem. Soc., 2013, **135**, 13400–13413

We report classical molecular dynamics (MD) simulations and combined quantum mechanics/molecular mechanics (QM/MM) calculations to elucidate the catalytic mechanism of the rate-determining amine oxidation step in the lysine-specific demethylase 1 (LSD1)-catalyzed demethylation of the histone tail lysine (H3K4), with flavin adenine dinucleotide (FAD) acting as cofactor. The oxidation of substrate lysine (sLys) involves the cleavage of an α-CH bond accompanied by the transfer of a hydride ion equivalent to FAD, leading to an imine intermediate.

A!

Comparison of treecodes for computing electrostatic potentials in charged particle systems with disjoint targets and sources

Henry A. Boateng [University of Michigan], Robert Krasny

J. Comp. Chem., **34**, 2159–2167, 2013.

In molecular simulations, it is sometimes necessary to compute the electrostatic potential at *M* target sites due to a disjoint set of *N*charged source particles. Direct summation requires *O*(*MN*) operations, which is prohibitively expensive when *M* and *N* are large. Here, we consider two alternative tree-based methods that reduce the cost. The standard particle-cluster treecode partitions the *N* sources into an octree and applies a far-field approximation, whereas a recently developed cluster-particle treecode instead partitions the *M* targets into an octree and applies a near-field approximation.

GTKDynamo: A PyMOL plug-in for QC/MM hybrid potential simulations

José Fernando R. Bachega [Universidade de São Paulo], Luís Fernando S. M. Timmers, Lucas Assirati,Leonardo R. Bachega, Martin J. Field,Troy Wymore

J. Comp. Chem., **34**, 2190–2196, 2013.

Despite their utility, however, these potentials are not always straightforward to apply since the extent of significant electronic structure changes occurring in the condensed phase process may not be intuitively obvious.To facilitate their use, we have developed an open-source graphical plug-in, GTKDynamo that links the PyMOL visualization program and the pDynamo QC/MM simulation library. This article describes the implementation of GTKDynamo and its capabilities and illustrates its application to QC/MM simulations.

S!

Theoretical study on isomerization and peptide bond cleavage at aspartic residue

Wichien Sang-aroon [Rajamangala University of Technology Isan], Vithaya Ruangpornvisuti

J. Mol.Mod., **19,** 3627-3636, 2013.

Isomerization and peptide bond cleavage at aspartic residue (Asp) in peptide models have been reported. In this study, the mechanisms and energies concerning the isomerization and peptide bond cleavage at Asp residue were investigated by the density functional theory (DFT) at B3LYP/6-311++G(d,p). The integral equation formalism-polarizable continuum model (IEF-PCM) was utilized to calculate solvation effect by single-point calculation of the gas-phase B3LYP/6-311++G(d,p)-optimized structure.

QM and QM/MM (Cont'd)

A coupled two-dimensional main chain torsional potential for protein dynamics: generation and implementation

Yongxiu Li, Ya Gao, Xuqiang Zhang, Xingyu Wang, Lirong Mou, LiLi Duan, Xiao He, Ye Mei, John Z. H. Zhang [East China Normal University]

J. Mol.Mod., **19,** 3647-3657, 2013.

Main chain torsions of alanine dipeptide are parameterized into coupled 2-dimensional Fourier expansions based on quantum mechanical (QM) calculations at M06 2X/aug-cc-pvtz//HF/6-31G** level. Solvation effect is considered by employing polarizable continuum model. Utilization of the M06 2X functional leads to precise potential energy surface that is comparable to or even better than MP2 level, but with much less computational demand. Parameterization of the 2D expansions is against the full main chain torsion space instead of just a few low energy conformations.

Relative Free Energies for Hydration of Monovalent Ions from QM and QM/MM Simulations

Bogdan Lev , Benoît Roux , and Sergei Yu. Noskov [The University of Calgary]

J. Chem. Theor. and Comp, **9**, 4165–4175, 2013.

Methods directly evaluating the hydration structure and thermodynamics of physiologically relevant cations (Na^+, K^+, Cl^-, etc.) have wide ranging applications in the fields of inorganic, physical, and biological chemistry. All-atom simulations based on accurate potential energy surfaces appear to offer a viable option for assessing the chemistry of ion solvation. Although MD and free energy simulations of ion solvation with classical force fields have proven their usefulness, a number of challenges still remain. Herein, we report the results from QM/MM free energy simulations of Na^+/K^+ and Cl^-/Br^- hydration where we simultaneously characterized the relative thermodynamics of ion solvation and changes in the solvation structure.

Effect of Geometry Optimizations on QM-Cluster and QM/MM Studies of Reaction Energies in Proteins

Sophie Sumner , Pär Söderhjelm , and Ulf Ryde [Lund University]

J. Chem. Theor. and Comp, **9**, 4205–4214, 2013.

We have examined the effect of geometry optimization on energies calculated with the quantum mechanical (QM) cluster, combined QM and molecular mechanics (QM/MM), and big-QM approaches (very large single-point QM calculations taken from QM/MM-optimized structures, including all atoms within 4.5 Å of the minimal active site, all buried charged groups in the protein, and truncations moved at least three residues away from the active site). We studied a simple proton-transfer reaction between His-79 and Cys-546 in the active site of [Ni,Fe] hydrogenase and optimize QM systems of 50 different sizes (56–362 atoms).

QM and QM/MM (Cont'd)

Computing pK_a Values with a Mixing Hamiltonian Quantum Mechanical/Molecular Mechanical Approach

Yang Liu , Xiaoli Fan , Yingdi Jin, Xiangqian Hu , and Hao Hu [The University of Hong Kong]

J. Chem. Theor. and Comp, **9**, 4257–4265, 2013.

Accurate computation of the pK_a value of a compound in solution is important but challenging. Here, a new mixing quantum mechanical/molecular mechanical (QM/MM) Hamiltonian method is developed to simulate the free-energy change associated with the protonation/deprotonation processes in solution. The mixing Hamiltonian method is designed for efficient quantum mechanical free-energy simulations by alchemically varying the nuclear potential, i.e., the nuclear charge of the transforming nucleus.

From Formamide to Purine: A Self-Catalyzed Reaction Pathway Provides a Feasible Mechanism for the Entire Process

Jing Wang, Jiande Gu, Minh Tho Nguyen, Greg Springsteen, and Jerzy Leszczynski [Jackson State University]

J. Phys. Chem. B., **117**, 9333–9342, 2013**.**

A formamide self-catalyzed mechanistic pathway that transforms formamide to purine through a five-membered ring intermediate has been explored by density functional theory calculations. The highlight of the mechanistic route detailed here is that the proposed pathway represents the simplest and lowest energy reaction pathway. All necessary reactants, including catalysts, are generated from a single initial compound, formamide. The most catalytically effective form of formamide is found to be the imidic acid isomer. The catalytic effect of formamide has been found to be much more significant than that of water.

Free Energies of Binding from Large-Scale First-Principles Quantum Mechanical Calculations: Application to Ligand Hydration Energies

Stephen J. Fox , Chris Pittock , Christofer S. Tautermann , Thomas Fox , Clara Christ , N. O. J. Malcolm , Jonathan W. Essex , and Chris-Kriton Skylaris [University of Southampton]

J. Phys. Chem. B., **117**, 9478–9485, 2013**.**

In this work, we investigate the use of large-scale quantum mechanical calculations from first-principles as a way of fully taking into account electronic effects in free-energy calculations. We employ a one-step free-energy perturbation (FEP) scheme from a molecular mechanical (MM) potential to a quantum mechanical (QM) potential as a correction to thermodynamic integration calculations within the MM potential. We use this approach to calculate relative free energies of hydration of small aromatic molecules.

Electron-Attachment-Induced DNA Damage: Instantaneous Strand Breaks

Emilie Cauët [Vrije Universiteit Brussel], Stuart Bogatko, Jacques Liévin, Frank De Proft, and Paul Geerlings

J. Phys. Chem. B., **117**, 9669–9676, 2013**.**

Low energy electron-attachment-induced damage in DNA, where dissociation channels may involve multiple bonds including complex bond rearrangements and significant nuclear motions, is analyzed here. Quantum mechanics/molecular mechanics (QM/MM) calculations reveal how rearrangements of electron density after vertical electron attachment modulate the position and dynamics of the atomic nuclei in DNA.

QM and QM/MM (Cont'd)

Electron-Hole Transfer in G-Quadruplexes with Different Tetrad Stacking Geometries: A Combined QM and MD Study

Christopher J. Lech, Anh Tuân Phan, and Maria-Elisabeth Michel-Beyerle , Alexander A. Voityuk [Universitat de Girona]

J. Phys. Chem. B., **117**, 9851–9856, 2013**.**

We identify a distinguished structure that allows for strong electronic coupling and thus enhanced molecular electric conductance. We also demonstrate the importance of sampling a large number of geometries when considering the bulk properties of such systems. Hole hopping within single G-tetrads is slower by at least two orders of magnitude than between stacked guanines; therefore, hole jumping within individual tetrads should not affect the hole mobility in G-quadruplexes.

Molecular Modeling Study of Dihydrofolate Reductase Inhibitors. Molecular Dynamics Simulations, Quantum Mechanical Calculations, and Experimental Corroboration

Rodrigo D. Tosso, Sebastian A. Andujar, Lucas Gutierrez, Emilio Angelina, Ricaurte Rodríguez, Manuel Nogueras, Héctor Baldoni, Fernando D. Suvire, Justo Cobo, and Ricardo D. Enriz [Universidad Nacional de San Luis]

J.Chem. Infor. and Mod. **53**, 2018–2032, 2013.

A molecular modeling study on dihydrofolate reductase (DHFR) inhibitors was carried out. By combining molecular dynamics simulations with semiempirical (PM6), ab initio, and density functional theory (DFT) calculations, a simple and generally applicable procedure to evaluate the binding energies of DHFR inhibitors interacting with the human enzyme is reported here, providing a clear picture of the binding interactions of these ligands from both structural and energetic viewpoints. A reduced model for the binding pocket was used.

Ligand Docking

Exploring Novel Modified Vitamin B_{12} as a Drug Carrier: Forecast from Density Functional Theory Modeling

Dorota Rutkowska-Zbik[Polish Academy of Sciences], Gabriela Mazur, Agnieszka Drzewiecka-Matuszek, Łukasz Orzeł, and Grażyna Stochel

J. Phys. Chem. B., **117**, 9655–9661, 2013**.**

Furthermore, the possibility of the formation of their conjugates with cisplatin is investigated. The proposed β-ligands may serve as bridging ligands, binding to the platin ion as N-donors. In parallel, the calculations are done for the previously synthetized B_{12}–cisplatin adduct with CN^- as a bridging ligand and are compared with available experimental data, allowing assessment of the applied computational protocol. A good agreement between the computed and experimental structural parameters is obtained. In each of the studied structures, the Co−β-ligand bond is weaker than the Pt−β-ligand bond.

Docking Challenge: Protein Sampling and Molecular Docking Performance

Khaled M. Elokely and Robert J. Doerksen [University of Mississippi]

J.Chem. Infor. and Mod. **53**, 1934–1945, 2013.

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Computational tools are essential in the drug design process, especially in order to take advantage of the increasing numbers of solved X-ray and NMR protein–ligand structures. Nowadays, molecular docking methods are routinely used for prediction of protein–ligand interactions and to aid in selecting potent molecules as a part of virtual screening of large databases. The improvements and advances in computational capacity in the past decade have allowed for further developments in molecular docking algorithms to address more complicated aspects such as protein flexibility.

Ligand Docking (Cont'd)

Molecular Simulations of Aromatase Reveal New Insights Into the Mechanism of Ligand Binding

Jiho Park, Luke Czapla, and Rommie E. Amaro [University of California]

J.Chem. Infor. and Mod. **53**, 1017–1025, 2013.

CYP19A1, also known as aromatase or estrogen synthetase, is the rate-limiting enzyme in the biosynthesis of estrogens from their corresponding androgens. Several clinically used breast cancer therapies target aromatase. In this work, explicitly solvated all-atom molecular dynamics simulations of aromatase with a model of the lipid bilayer and the transmembrane helix are performed. The dynamics of aromatase and the role of titration of an important amino acid residue involved in aromatization of androgens are investigated via two 250-ns long simulations.

Improved Ligand Binding Energies Derived from Molecular Dynamics: Replicate Sampling Enhances the Search of Conformational Space

Marc Adler [Elan Pharmaceuticals]and Paul Beroza

J.Chem. Infor. and Mod. **53**, 1017–1025, 2013.

Does a single molecular trajectory provide an adequate sample conformational space? Our calculations indicate that for Molecular Mechanics - Poisson–Boltzmann Surface Area (MM-PBSA) measurement of protein ligand binding, a single molecular dynamics trajectory does not provide a representative sampling of phase space. For a single trajectory, the binding energy obtained by averaging over a number of molecular dynamics frames in an equilibrated system will converge after an adequate simulation time. A separate trajectory with nearly identical starting coordinates (1% randomly perturbed by 0.001 Å), however, can lead to a significantly different calculated binding energy.

Cavities Tell More than Sequences: Exploring Functional Relationships of Proteases via Binding Pockets

Serghei Glinca and Gerhard Klebe [University of Marburg]

J.Chem. Infor. and Mod. **53**, 2082–2092, 2013.

Computational approaches play an increasingly important role for the analysis and prediction of selectivity profiles. As most of the successfully administered small molecule drugs bind in depressions on the surface of proteins, physicochemical properties of the pocket-exposed amino acids play a central role in ligand recognition during the binding event. Cavbase is an approach to describe binding sites in terms of the exposed physicochemical properties and to compare them independent of their sequence and fold homology.

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3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 44,September 2013.

1–12 **Molecular modeling and simulation of FabG, an enzyme involved in the fatty acid pathway of *Streptococcus pyogenes* ,**Rajamohmed Beema Shafreen, Shunmugiah Karutha Pandian [Alagappa University]

See Applications / Homology Modeling.

13–25 **Theoretical studies on the binding of rhenium(I) complexes to inducible nitric oxide synthase ,**Bruno L. Oliveira [Universidade Técnica de Lisboa] , Irina S. Moreira , Pedro A. Fernandes, Maria J. Ramos , Isabel Santos , João D.G. Correia

See Applications / Enzyme Catalysis.

26–37 **Molecular basis for benzimidazole resistance from a novel β-tubulin binding site model ,**Rodrigo Aguayo-Ortiz , Oscar Méndez-Lucio , Antonio Romo-Mancillas , Rafael Castillo , Lilián Yépez-Mulia , José L. Medina-Franco , Alicia Hernández-Campos Universidad Nacional Autónoma de México (UNAM)]

See Applications / Ligand Binding.

38–44 **Elucidating binding modes of zuonin A enantiomers to JNK1 via in silico methods** Daniel W. Dykstra , Kevin N. Dalby , Pengyu Ren [University of Texas at Austin]

See Applications / Ligand Binding.

45–49 **Studies on argon collisions with smooth and rough tungsten surfaces ,**M.S. Ozhgibesov[National Cheng Kung University] , T.S. Leu , C.H. Cheng , A.V. Utkin

The aim of this work is to investigate argon scattering behaviors on the smooth and rough tungsten surfaces. Current work deals with numerical simulation of nanoscale heat transfer process accompanying with rarefied gas–solid substrate interactions using molecular dynamics (MD) method.

50–64 **Insights into the structure–function relationship of disease resistance protein HCTR in maize (*Zea mays* L.): A computational structural biology approach ,**Budheswar Dehury , Mousumi Sahu , Mahesh Chandra Patra , Kishore Sarma , Jagajjit Sahu ,Priyabrata Sen , Mahendra Kumar Modi , Manabendra Dutta Choudhury , Madhumita Barooah [Assam Agricultural University]

See Applications / Enzyme Catalysis.

65–83 **Comprehensive 3D-QSAR and binding mode of BACE-1 inhibitors using R-group search and molecular docking ,**Dandan Huang, Yonglan Liu, Bozhi Shi, Yueting Li, Guixue Wang, Guizhao Liang [Chongqing University]

See Applications / Quantitative Structure-Activity Relation.

Journal of Computational Chemistry, 34 (24), September 2013.

2055–2064 **Computational gibberellin-binding channel discovery unraveling the unexpected perception mechanism of hormone signal by gibberellin receptor ,**Ge-Fei Hao, Sheng-Gang Yang, Guang-Fu Yang, Chang-Guo Zhan [University of Kentucky]

See Applications / Ligand Binding.

2065–2078 **A parallel finite element simulator for ion transport through three-dimensional ion channel systems ,**Bin Tu, Minxin Chen, Yan Xie, Linbo Zhang, Bob Eisenberg, Benzhuo Lu [Chinese Academy of Sciences, Beijing]

See Applications / Bioinformatics.

2079–2090 **Comparative analysis of the performance of commonly available density functionals in the determination of geometrical parameters for copper complexes ,**Sérgio F. Sousa, Gaspar R. P. Pinto,António J. M. Ribeiro, João T. S. Coimbra, PedroA.Fernandes, Maria João Ramos [Universidade do Porto]

In this study, a set of 50 transition-metal complexes of Cu(I) and Cu(II), were used in the evaluation of 18 density functionals in geometry determination. In addition, 14 different basis sets were considered, including four commonly used Pople's all-electron basis sets; four basis sets including popular types of effective-core potentials: Los Alamos, Steven-Basch-Krauss, and Stuttgart-Dresden; and six triple-ζ basis sets.

2091–2099 ***Ab Initio* Diabatic energies and dipole moments of the electronic states of RbLi molecule** Riadh Dardour [Université de Monastir], Héla Habli, Brahim Oujia, Florent Xavier Gadéa

For all states dissociating below the ionic limit $Li^- Rb^+$, we perform a diabatic study for $^1\Sigma^+$ electronic states dissociating into Rb (5s, 5p, 4d, 6s, 6p, 5d, 7s, 4f) + Li (2s, 2p, 3s). Furthermore, we present the diabatic results for the 1–11 $^3\sigma$, 1–8 $^{1,3}\Pi$, and 1–4 $^{1,3}\Delta$ states.

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2100–2120 **Multiscale geometric modeling of macromolecules II: Lagrangian representation ,**Xin Feng, Kelin Xia, Zhan Chen,Yiying Tong, Guo-Wei Wei [Michigan State University,]

Geometric modeling of biomolecules plays an essential role in the conceptualization of biolmolecular structure, function, dynamics, and transport. In this work, we present a family of variational multiscale geometric models for macromolecular systems.

2121–2132 **QSARINS: A new software for the development, analysis, and validation of QSAR MLR models ,**Paola Gramatica [University of Insubria], Nicola Chirico, Ester Papa, Stefano Cassani, Simona Kovarich

See Methodology / QSAR.

Journal of Computational Chemistry, 34 (25), September 2013.

2135–2145 **CHARMM36 all-atom additive protein force field: Validation based on comparison to NMR data ,**Jing Huang, Alexander D. MacKerell Jr [University of Maryland]

See Applications / Protein Dynamics.

2146–2151 **Evaluation of electrostatic descriptors for predicting crystalline density ,**Betsy M. Rice [US Army Research Laboratory], Edward F. C. Byrd

This study evaluates the importance of electrostatic corrections to earlier quantum-mechanically based methods to predict crystal densities of neutral and ionic molecular energetic materials.

2152–2158 **Transition polarizability model of induced resonance Raman optical activity ,**Shigeki Yamamoto, Petr Bouř [Academy of Sciences, 16610 Prague,]

Induced resonance Raman optical activity (IRROA) proved to be a very sensitive method to detect molecular chirality. It is exhibited, for example, by complexes of lanthanides with chiral alcohols or ketones.

2159–2167 **Comparison of treecodes for computing electrostatic potentials in charged particle systems with disjoint targets and source ,**Henry A. Boateng [University of Michigan], Robert Krasny

See Methodology / QM and QM/MM.

2168–2177 **Auxiliary basis sets for density-fitting second-order Møller–Plesset perturbation theory: Weighted core-valence correlation consistent basis sets for the 4*d* elements Y–Pd ,**J. Grant Hill [University of Glasgow]

Auxiliary basis sets (ABS) specifically matched to the cc-pwCV*n*Z-PP and aug-cc-pwCV*n*Z-PP orbital basis sets (OBS) have been developed and optimized for the 4*d* elements Y-Pd at the second-order Møller-Plesset perturbation theory level. Calculation of the core-valence electron correlation energies for small to medium sized transition metal complexes demonstrates that the error due to the use of these new sets in density fitting is three to four orders of magnitude smaller than that due to the OBS incompleteness, and hence is considered negligible

2178–2189 **Global optimization of parameters in the reactive force field ReaxFF for SiOH ,**Henrik R. Larsson, Adri C. T. van Duin, Bernd Hartke [Christian-Albrechts-University]

We have used unbiased global optimization to fit a reactive force field to a given set of reference data. Specifically, we have employed genetic algorithms (GA) to fit ReaxFF to SiOH data, using an in-house GA code that is parallelized across reference data items via the message-passing interface (MPI).

2190–2196 **GTKDynamo: A PyMOL plug-in for QC/MM hybrid potential simulations ,**José Fernando R. Bachega [Universidade de São Paulo], Luís Fernando S. M. Timmers, Lucas Assirati,Leonardo R. Bachega, Martin J. Field,Troy Wymore

See Applications / QM and QM/MM.

2197–2211 **GALAMOST: GPU-accelerated large-scale molecular simulation toolkit ,**You-Liang Zhu, Hong Liu, Zhan-Wei Li,Hu-Jun Qian, Giuseppe Milano, Zhong-Yuan Lu [Jilin University]

See Applications / Bioinformatics.

2212–2221 **VinaMPI: Facilitating multiple receptor high-throughput virtual docking on high-performance computers** Sally R. Ellingson, Jeremy C. Smith, Jerome Baudry [University of Tennessee]

See Applications / Bioinformatics.

Journal of Molecular Modeling, 19 (9), September 2013.

3463-3469 **A method for in silico identification of SNAIL/SLUG DNA binding potentials to the E-box sequence using molecular dynamics and evolutionary conserved amino acids ,**Jeremy W. Prokop [The University of Akron], Yuanjie Liu, Amy Milsted, Hongzhuang Peng, Frank J. Rauscher III

See Applications / Nucleic Acids.

3471-3479 **DFT and MP2 study of low barrier proton transfer in hydrazide schiff base tautomers via water bridges and in the gas ,**Hossein Tavakol [Isfahan University of Technology], Hossein Farrokhpour

MP2 and DFT studies were performed on the tautomers of N′-ethylideneacetohydrazide in different environments including gas phase, continuum solvent and microhydrated environment. The ground electronic state structures of the tautomers were optimized at the MP2 and B3LYP levels of theory using 6-311++G(d,p), separately.

3481-3489 **Thermal, electronic and ductile properties of lead-chalcogenides under pressure** ,Dinesh C. Gupta, Idris Hamid Bhat [Jiwaji University]

Fully relativistic pseudo-potential ab-initio calculations have been performed to investigate the high pressure phase transition, elastic and electronic properties of lead-chalcogenides including the less known lead polonium.

3491-3499 **Looking for high energy density compounds among polynitraminepurines ,**Ting Yan, Guangdong Sun, Weijie Chi, Butong Li [Shanxi Normal University], Haishun Wu

A series of purine derivatives with nitramine groups are calculated by using density functional theory (DFT). The molecular theory density, heats of formation, bond dissociation energies and detonation performance are investigated at DFT-B3LYP/6-311G** level.

3501-3506 **Reaction mechanism of $CH_3M{\equiv}MCH_3$ (M=C, Si, Ge) with C_2H_4: [2+1] or [2+2] cycloaddition?** Suhong Huo, Xiaoyan Li, Yanli Zeng, Shijun Zheng, Lingpeng Meng [Hebei Normal University]

The mechanism of the cycloaddition reaction $CH_3M{\equiv}MCH_3$ (M=C, Si, Ge) with C_2H_4 has been studied at the CCSD(T)/6-311++G(d,p)//MP2/6-311++G(d,p) level. Vibrational analysis and intrinsic reaction coordinate (IRC), calculated at the same level, have been applied to validate the connection of the stationary points.

3507-3515 **Computational nanochemistry study of the molecular structure and properties of ethambutol,** Guillermo Salgado-Morán, Samuel Ruiz-Nieto, Lorena Gerli-Candia, Norma Flores-Holguín, Alejandra Favila-Pérez, Daniel Glossman-Mitnik [Centro de Investigación en Materiales Avanzados]

The M06 family of density functionals was employed to calculate the molecular structure and properties of the ethambutol molecule. Besides determination of molecular structures, UV–vis spectra were computed using TD-DFT in the presence of a solvent and the results compared with available experimental data.

3517-3527 **In silico discrimination of nsSNPs in*hTERT* gene by means of local DNA sequence context and regularity ,**C. George Priya Doss [VIT University], Chiranjib Chakraborty, B. Rajith, N. Nagasundaram

See Applications / Nucleic Acids.

3529-3535 **A comparative study of the aromaticity of pyrrole, furan, thiophene, and their aza-derivatives** ,Kalbinur Najmidin, Ablikim Kerim [Xinjiang University], Paruza Abdirishit, Horigul Kalam, Tursungul Tawar

The relative aromaticity of pyrrole, furan, thiophene, and their aza-derivatives has been examined using TRE (topological resonance energy), MRE (magnetic resonance energy), ring current (RC), and ring current diamagnetic susceptibility (χ_G) methods.

3537-3542 **DFT calculation of the electronic properties of fluorene-1,3,4-thiadiazole oligomers ,**Nora Aydeé Sánchez-Bojorge, Luz María Rodríguez-Valdez, Norma Flores-Holguín [NANOCOSMOS Virtual Lab]

Thiadiazole derivatives have been widely employed in the areas of pharmaceutical, agricultural, industrial, and polymer chemistry. The electronic and molecular structures of thiadiazoles are of interest because they have an equal number of valence electrons and similar molecular structures to thiophenes, which are currently used in the construction of organic solar cells due to their relatively high hole mobilities and good light-harvesting properties.

3543-3549 **Theoretical study of the pre- and post-translational effects of adenine and thymine tautomers and methyl derivatives ,**Noel Gardner, David Magers, Glake Hill Jr. [Jackson State University]

See Applications / Nucleic Acids.

3551-3568 **A new theoretical analysis of the cooperative effect in T-shaped hydrogen complexes of $C_nH_m{\cdots}HCN{\cdots}HW$ with n = 2, m = 2 or 4, and W = F or CN ,**Boaz G. Oliveira [Universidade Federal da Bahia], Tamires F. Costa, Regiane C. M. U. Araújo

In this theoretical work, a new idea about cooperativity in intermolecular clusters of $C_nH_m{\cdots}HCN{\cdots}HW$ stabilized by hydrogen bonds composed by lone-electron pairs (nitrogen) and π clouds (C = C and C ≡ C) as proton acceptors is developed.

3569-3580 **Modeling the physisorption of bisphenol A on graphene and graphene oxide ,**Diego Cortés-Arriagada [Universidad de Santiago de Chile], Luis Sanhueza, Mireya Santander-Nelli

The physisorption of bisphenol A (BPA) on pristine and oxidized graphene was studied theoretically via calculations performed at the PBE-D3 level (including dispersion force corrections). Three stable conformations of BPA on graphene were found. A lying-down configuration was energetically favored because the presence of π–π stacking and dispersion forces increased interactions.

3581-3589 **Structure guided inhibitor designing of CDK2 and discovery of potential leads against cancer** ,Arun Kumar V.A [Sathyabama University], Keshav Mohan, Syed Riyaz

See Applications / Medicinal Chemmistry and Drug Design.

3591-3602 **Molecular modeling of the piezoelectric effect in the ferroelectric polymer poly(vinylidene fluoride) (PVDF) ,**Vladimir S. Bystrov [University of Aveiro], Ekaterina V. Paramonova, Igor K. Bdikin, Anna V. Bystrova, Robert C. Pullar,Andrei L. Kholkin

In this work, computational molecular modeling and exploration was applied to study the nature of the negative piezoelectric effect in the ferroelectric polymer polyvinylidene fluoride (PVDF), and the results confirmed by actual nanoscale measurements.

3603-3610 **Oxygen doped SiC nanocrystals: first principles study of the optical properties** ,Masoud Bezi Javan[Golestan University]

We have studied a typical spherical SiC nanocrystal with a diameter of 1.2 nm ($Si_{43}C_{44}H_{76}$) using linear combination of atomic orbitals in combination with pesudopotential density functional calculation. The role of fluorine and oxygen impurities was investigated on the electronic and optical properties of the $Si_{43}C_{44}H_{76}$ nanocrystal.

3611-3618 **Theoretical investigation of the selectivity in intramolecular cyclizations of some 2'–aminochalcones to dihydroquinolin–8–ones and indolin–3–ones ,**Andres Reyes, Paola Andrea Cuervo, Fabian Orozco, Rodrigo Abonia, Mario Duque-Noreña, Patricia Pérez, Eduardo Chamorro [Universidad Andres Bello]

The selectivity of the intramolecular cyclizations of a series of 2'–aminochalcones was investigated with an approach that combines spin–polarized conceptual density functional theory and energy calculations.

3619-3626 **Predicting the preferred conformations of luteolin-4′-O-β-D-glucoside in gas phase: a comparison of two computational approaches** ,Yongzhi Li, Xiuhua Liu, Dong Chen, Zhichao Wei, Bo Liu [Henan University]

A tree-step computational approach has been applied to determine the lowest-energy conformers of luteolin-4′-O-β-D-glucoside (L4′G). Fifty-seven starting structures of the L4′G have been built, and then by performing with density functional theory (DFT) optimizations and second-order Møller-Plesset (MP2) calculations.

substituents has a significant effect upon the most positive electrostatic potential on the surface of the interacting halogen atom.

3779-3791 **Structural and phylogenetic basis for the classification of group III phospholipase A_2 ,**Gururao Hariprasad [All India Institute of Medical Sciences], Alagiri Srinivasan, Reema Singh

Secretory phospholipase A_2 (PLA_2) catalyses the hydrolysis of the *sn-2* position of glycerophospholipids to liberate arachidonic acid, a precursor of eicosanoids, that are known mediators of inflammation. The group III PLA_2 enzymes are present in a wide array of organisms across many species with completely different functions.

3793-3798 **NH_3 on a BC_3 nanotube: effect of doping and decoration of aluminum** Ali Ahmadi Peyghan, Mohammad Bigdeli Tabar, Jamal Kakemam [Islamic Azad University]

The adsorption of the NH_3 molecule was investigated on pristine, Al-doped and Al-decorated BC_3nanotubes (BC_3NT) using density functional theory calculations. It was found that NH_3 prefers to be adsorbed on a B atom of the tube wall, releasing energy of 1.02 eV.

3799-3803 **Electron density reactivity indexes of the tautomeric/ionization forms of thiamin diphosphate** Gonzalo A. Jaña, Eduardo J. Delgado [Universidad de Concepción]

The generation of the highly reactive ylide in thiamin diphosphate catalysis is analyzed in terms of the nucleophilicity of key atoms, by means of density functional calculations at X3LYP/6–31++G(d,p) level of theory.

3805-3812 **Electronic structure and optical properties of Cu-doping and Zn vacancy impurities in ZnTe** ,Qing-Fang Li, Ge Hu [Chongqing University], Qing She, Jing Yao, Wen-Jiang Feng

The geometric structures of perfect ZnTe, that with Zn vacancy ($Zn_{0.875}Te$), and Cu-doped ZnTe ($Zn_{0.875}Cu_{0.125}Te$) were optimized using the pseudopotential plane wave (PP-PW) method based on the density functional theory (DFT) within generalized gradient approximation (GGA).

3813-3819 **Molecular dynamics simulations of hydrogen storage capacity of few-layer grapheme ,**Cheng-Da Wu, Te-Hua Fang, Jian-Yuan Lo, Yu-Lun Feng[National Kaohsiung University of Applied Sciences]

The adsorption of molecular hydrogen on few-layer graphene (FLG) structures is studied using molecular dynamics simulations. The interaction between graphene and hydrogen molecules is described by the Lennard-Jones potential.

3821-3829 **A theoretical study on the halogen bonding interactions of C_6F_5I with a series of group 10 metal monohalides** ,Na Cheng, Yongjun Liu [Shandong University], Changqiao Zhang, Chengbu Liu

The halogen bonding interactions between C_6F_5I and a series of transition metal monohalides *trans*-[M(X)(2-C_5NF_4)-$(PR_3)_2$] (M = Ni, Pd, Pt; X = F, Cl, Br; R = Me, Cy) have been studied with quantum chemical calculations. Optimized geometries of the halogen bonding complexes indicate that angles C_1-I···X are basically linear (178–180°) and angles I···X-M mainly range from 90 to 150°.

3893-3899 **Molecular dynamics simulations of void defects in the energetic material HMX** ,Xiao Hui Duan, Wen Peng Li, Chong Hua Pei, Xiao Qing Zhou [Southwest University of Science and Technology]

A molecular dynamics (MD) simulation was carried out to characterize the dynamic evolution of void defects in crystalline octahydro-1, 3, 5, 7-tetranitro-1, 3, 5, 7-tetrazocine (HMX). Different models were constructed with the same concentration of vacancies (10 %) to discuss the size effects of void. Energetic ground state properties were determined by annealing simulations.

3901-3910 **An information-theoretic classification of amino acids for the assessment of interfaces in protein–protein docking** ,Christophe Jardin, Arno G. Stefani, Martin Eberhardt, Johannes B. Huber, Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

See Applications / protein-protien Interaction.

3911-3923 **Screening of different computational models for the preparation of sol–gel imprinted materials** Elmer-Rico E. Mojica [Pace University]

Different computational models were used and screened to find a rational way in selecting the appropriate functional silane monomer for the best molecular imprinted xerogel (MIX) formulation. Several functional silane monomers were used and allowed to react with a template model, tetracycline (TC).

3925-3930 **Temperature dependence of the polarization and the dielectric constant near the paraelectric-ferroelectric transitions in $BaTiO_3$** ,H. Yurtseven [Middle East Technical University], A. Kiraci

Temperature dependences of the spontaneous polarization and the dielectric constant are calculated near the paraelectric-ferroelectric (cubic-tetragonal) transition in $BaTiO_3$ using our mean field model.

3931-3939 **Equilibrium and folding simulations of NS4B H2 in pure water and water/2,2,2-trifluoroethanol mixed solvent: examination of solvation models** ,Man Guo, Ye Mei [East China Normal University]

See Applications / Protein Dynamics.

3941-3946 **Fluorination of BC_3 nanotubes: DFT studies** ,Ali Ahmadi Peyghan, Maziar Noei [Islamic Azad University]

We have studied the adsorption of atomic and molecular fluorines on a BC_3 nanotube by using density functional calculations. It was found that the adsorption of atomic fluorine on a C atom of the tube surface is energetically more favorable than that on a B atom by about 0.97 eV.

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1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

Homogeneous Ice Nucleation at Moderate Supercooling from Molecular Simulation

E. Sanz, C. Vega, J. R. Espinosa, R. Caballero-Bernal, J. L. F. Abascal, and C. Valeriani [Universidad Complutense de Madrid]

J. Am. Chem. Soc., 2013, **135**, 15008–15017

Among all of the freezing transitions, that of water into ice is probably the most relevant to biology, physics, geology, or atmospheric science. In this work, we investigate homogeneous ice nucleation by means of computer simulations. We evaluate the size of the critical cluster and the nucleation rate for temperatures ranging between 15 and 35 K below melting. We use the TIP4P/2005 and the TIP4P/ice water models. Both give similar results when compared at the same temperature difference with the model's melting temperature.

Molecular modeling of enzyme attachment on AFM probes

Guedmiller S. Oliveira [Federal University of São Carlos], Fabio L. Leite ,Adriano M. Amarante ,Eduardo F. Franca ,Richard A. Cunha, James M. Briggs ,Luiz C.G. Freitas

J. Mol.Graph. and Mod., **45,** 128–136, 2013.

The immobilization of enzymes on atomic force microscope tip (AFM tip) surface is a crucial step in the development of nanobiosensors to be used in detection process. In this work, an atomistic modeling of the attachment of the acetyl coenzyme A carboxylase (ACC enzyme) on a functionalized AFM tip surface is proposed. Using electrostatic considerations, suitable enzyme–surface orientations with the active sites of the ACC enzyme available for interactions with bulk molecules were found.

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Water and Solvation

Molecular Properties by Quantum Monte Carlo: An Investigation on the Role of the Wave Function Ansatz and the Basis Set in the Water Molecule

Andrea Zen, Ye Luo, Sandro Sorella [La Sapienza—Università di Roma], and Leonardo Guidoni

J. Chem. Theor. and Comp, **9**, 4332–4350, 2013.

Quantum Monte Carlo methods are accurate and promising many body techniques for electronic structure calculations which, in the last years, are encountering a growing interest thanks to their favorable scaling with the system size and their efficient parallelization, particularly suited for the modern high performance computing facilities. In this paper, we extensively analyze, using different variational ansatzes, several properties of the water molecule, namely, the total energy, the dipole and quadrupole momenta, the ionization and atomization energies, the equilibrium configuration, and the harmonic and fundamental frequencies of vibration.

On the Behavior of Water at Subfreezing Temperatures in a Protein Crystal: Evidence of Higher Mobility Than in Bulk Water

Dongqi Wang, Anja Böckmann, Jožica Dolenc, Beat H. Meier, and Wilfred F. van Gunsteren[Universite de Lyon]

J. Phys. Chem. B., **117**, 11433-11447, 2013**.**

NMR experiments have shown that water molecules in the crystal of the protein Crh are still mobile at temperatures well below 273 K. In order to investigate this water anomaly, a molecular dynamics (MD) simulation study of crystalline Crh was carried out to determine the mobility of water in this crystal. The simulations were carried out at three temperatures, 150, 200, and 291 K. Simulations of bulk water at these temperatures were also done to obtain the properties of the simple point charge (SPC) water model used at these temperatures and to allow a comparison of the properties of water in the Crh crystal with those of bulk water at the same temperatures.

Molecular Dynamics Simulations of Water Sorption in a Perfluorosulfonic Acid Membrane

Kevin B. Daly, Jay B. Benziger, Pablo G. Debenedetti, and Athanassios Z. Panagiotopoulos [Princeton University

J. Phys. Chem. B., **117**, 12649–12660, 2013**.**

Atomistic molecular dynamics simulations are reported over a wide range of water contents and temperatures to obtain a better understanding of the structural and transport aspects of water sorption in Nafion, a perfluorosulfonic acid membrane, under equilibrium conditions. For the short Nafion chains studied, good agreement is found between the water sorption isotherms from simulations and experiments at intermediate hydration ($2 \lesssim \lambda \lesssim 7$, where λ is the number of water molecules per sulfonate group), suggesting that, in that range, the isotherm is insensitive to effects of polymer chain relaxation.

Medicinal Chemistry and Drug Design

Investigation of silent information regulator 1 (Sirt1) agonists from Traditional Chinese Medicine

Kuan-Chung Chen, Yi-Ru Jian, Mao-Feng Sun, Tung-Ti Chang, Cheng-Chun Lee & Calvin Yu-Chian Chen [Asia University]

J. Biomol. Stru. and Dyn., ***31****(11)*, 1207-1218, *2013.*

Silent information regulator 1 (Sirt1), a class III nicotinamide adenine dinucleotide dependent histone deacetylases, is important in cardioprotection, neuroprotection, metabolic disease, calorie restriction, and diseases associated with aging. TCM compounds such as (S)-tryptophan-betaxanthin, 5-O-feruloylquinic acid, and RosA exhibited good binding affinity across different computational methods, and their drug-like potential were validated by MD simulation. Docking poses indicate that the carboxylic group of the three candidates generated H-bonds with residues in the protein chain from Ser441 to Lys444 and formed H-bond, π–cation interactions, or hydrophobic contacts with Phe297 and key active residue, His363.

Han ethnicity-specific type 2 diabetic treatment from traditional Chinese medicine?

Kuan-Chung Chen, Su-Sen Chang, Fuu-Jen Tsai & Calvin Yu-Chian Chen[China Medical University Hospita]

J. Biomol. Stru. and Dyn., ***31****(11)*, 1219-1235, *2013.*

Insulin-degrading enzyme (IDE) gene is one of the type 2 diabetes mellitus susceptibility genes specific to the Han Chinese population. IDE, a zinc-metalloendopeptidase, is a potential target for controlling insulin degradation. Potential lead compounds for IDE inhibition were identified from traditional Chinese medicine (TCM) through virtual screening and evaluation of their pharmacokinetic properties of absorption, distribution, metabolism, excretion, and toxicity. Molecular dynamics (MD) simulation was performed to validate the stability of complexes from docking simulation.

Design of e-pharmacophore models using compound fragments for the *trans*-sialidase of *Trypanosoma cruzi*: Screening for novel inhibitor scaffolds

Bill R. Miller III, Adrian E. Roitberg [University of Florida]

J. Mol.Graph. and Mod., **45,** 84–97, 2013.

S!

Chagas' is a fatal disease that affects millions of people worldwide. The lack of safe and effective treatments for Chagas' highlights the need for the discovery of new drugs to fight the disease. *Trypanosoma cruzi*, the parasitic cause of Chagas' disease, synthesizes a *trans*-sialidase (TcTS) enzyme responsible for the transfer of sialic acids from the host cell surface to glycoconjugates on the parasitic cell surface. TcTS has no human analogs and is vital to the life cycle of *T. cruzi*, making TcTS an important enzyme for drug design against Chagas' disease.

Identification of adenine nucleotide translocase 4 inhibitors by molecular docking

Wai-Yee Leung ,Takashi Hamazaki ,David A. Ostrov ,Naohiro Terada [University of Florida College of Medicine]

J. Mol.Graph. and Mod., **45,** 173–179, 2013.

The protein adenine nucleotide translocase (ANT) is localized in the mitochondrial inner membrane and plays an essential role in transporting ADP into the mitochondrial matrix and ATP out from the matrix for cell utilization. In mammals there are four paralogous ANT genes, of which ANT4 is exclusively expressed in meiotic germ cells. In this study, we aimed to identify candidate compounds that can selectively inhibit ANT4 activity over the other ANTs.

Medicinal Chemistry and Drug Design (Cont'd)

Bioisosteric approach in designing new monastrol derivatives: An investigation on their ADMET prediction using in silico derived parameters

Syed Fahad Hassan ,Umer Rashid [The University of Lahore,],Farzana Latif Ansari ,Zaheer Ul-Haq

J. Mol.Graph. and Mod., **45,** 202–210, 2013.

Medicinal chemists are facing an increasing challenge to deliver safer and more effective medicines. In this investigation, a bioisosteric approach was applied that resulted in the replacement of C-5 carbonyl of monastrol with thio-carbonyl. Further lead optimization of drug-like properties was evaluated through in silico predictions by using ADMET predictor software. This minor structural modification resulted in upgraded human effective jejunal permeability (Peff) and improved permeability in Madin–Darby canine kidney (MDCK) cells.

Discovery of New Inhibitors of *Mycobacterium tuberculosis* InhA Enzyme Using Virtual Screening and a 3D-Pharmacophore-Based Approach

Ivani Pauli, Ricardo N. dos Santos, Diana C. Rostirolla, Leonardo K. Martinelli, Rodrigo G. Ducati, Luís F. S. M. Timmers, Luiz A. Basso, Diógenes S. Santos, Rafael V. C. Guido, Adriano D. Andricopulo, and Osmar Norberto de Souza [Modelagem e Simulação de Biossistemas – LABIO]

J.Chem. Infor. and Mod. **53**, 2390–2401, 2013.

S!

Mycobacterium tuberculosis InhA (*Mt*InhA) is an attractive enzyme to drug discovery efforts due to its validation as an effective biological target for tuberculosis therapy. In this work, two different virtual-ligand-screening approaches were applied in order to identify new InhA inhibitors' candidates from a library of ligands selected from the ZINC database. First, a 3-D pharmacophore model was built based on 36 available *Mt*InhA crystal structures. By combining structure-based and ligand-based information, four pharmacophoric points were designed to select molecules able to satisfy the binding features of *Mt*InhA substrate-binding cavity.

Application of Computer-Aided Drug Repurposing in the Search of New Cruzipain Inhibitors: Discovery of Amiodarone and Bromocriptine Inhibitory Effects

Carolina L. Bellera, Darío E. Balcazar, Lucas Alberca, Carlos A. Labriola, Alan Talevi [National University of La Plata], and Carolina Carrillo

J.Chem. Infor. and Mod. **53**, 2402–2408, 2013.

Cruzipain (Cz) is the major cystein protease of the protozoan *Trypanosoma cruzi*, etiological agent of Chagas disease. From a 163 compound data set, a 2D-classifier capable of identifying Cz inhibitors was obtained and applied in a virtual screening campaign on the DrugBank database, which compiles FDA-approved and investigational drugs. Fifty-four approved drugs were selected as candidates, four of which were acquired and tested on Cz and *T.*

Discovery of New Selective Human Aldose Reductase Inhibitors through Virtual Screening Multiple Binding Pocket Conformations

Ling Wang, Qiong Gu [Sun Yat-Sen University], Xuehua Zheng, Jiming Ye, Zhihong Liu, Jiabo Li, Xiaopeng Hu, Arnold Hagler, and Jun Xu

J.Chem. Infor. and Mod. **53**, 2409–2422, 2013.

A!

Aldose reductase reduces glucose to sorbitol. It plays a key role in many of the complications arising from diabetes. Thus, aldose reductase inhibitors (ARI) have been identified as promising therapeutic agents for treating such complications of diabetes, as neuropathy, nephropathy, retinopathy, and cataracts. In this paper, a virtual screening protocol applied to a library of compounds in house has been utilized to discover novel ARIs. IC_{50}'s were determined for 15 hits that inhibited ALR2 to greater than 50% at 50 μM, and ten of these have an IC_{50} of 10 μM or less, corresponding to a rather substantial hit rate of 14% at this level.

Medicinal Chemistry and Drug Design (Cont'd)

Structurally Conserved Binding Sites of Hemagglutinin as Targets for Influenza Drug and Vaccine Development

Muhammad Yusuf, Janez Konc, Choi Sy Bing, Joanna Trykowska Konc, Nurul Bahiyah Ahmad Khairudin, Dusanka Janezic [National Institute of Chemistry, Ljubljana], and Habibah A. Wahab

J.Chem. Infor. and Mod. **53**, 2423–2436, 2013.

ProBiS is a new method to identify the binding site of protein through local structural alignment against the nonredundant Protein Data Bank (PDB), which may result in unique findings compared to the energy-based, geometry-based, and sequence-based predictors. In this work, binding sites of Hemagglutinin (HA), which is an important target for drugs and vaccines in influenza treatment, have been revisited by ProBiS. For the first time, the identification of conserved binding sites by local structural alignment across all subtypes and strains of HA available in PDB is presented. ProBiS finds three distinctive conserved sites on HA's structure (named Site 1, Site 2, and Site 3).

Polymer Micelle Assisted Transport and Delivery of Model Hydrophilic Components inside a Biological Lipid Vesicle: A Coarse-Grain Simulation Study

Goundla Srinivas [North Carolina State A&T University], Ram V. Mohan, and Ajit D. Kelkar

J. Phys. Chem. B., **117**, 12095–12104, 2013**.**

Understanding drug transportation and delivery mechanism from a molecular viewpoint is essential to find better treatment pathways. We study the interaction of polymeric micelle with DPPC lipid vesicles in detail. In order to facilitate hydrophilic drug transportation study, a primitive CG model for hydrophilic drug component is used. Extensive simulations carried out over hundreds of nanoseconds demonstrate successful encapsulation, transportation of hydrophilic components by patchy polymeric micelles. Results show the polymeric micelle releases a significant portion of hydrophilic contents inside the lipid vesicle.

Quantitative Structure-Activity Relations

3D-QSAR analysis of TRPV1 inhibitors reveals a pharmacophore applicable to diverse scaffolds and clinical candidates

Rajendra Kristam ,Vinod Parmar ,Vellarkad N. Viswanadhan[Jubilant Biosys Limited]

J. Mol.Graph. and Mod., **45,** 157–172, 2013.

TRPV1 (Transient Receptor Potential Vanilloid Type 1) receptor, a member of Transient Receptor Potential Vanilloid subfamily of ion channels, occurs in the peripheral and central nervous system, and plays a key role in transmission of pain. Consequently, this has been the target for discovery of several pain relieving agents which have undergone clinical trials. Herein, we describe a 3D-QSAR model ($n = 62$; $R^2 = 0.9$ and $Q^2 = 0.75$) developed from the piperazinyl-aryl series of compounds and a novel 5-point pharmacophore model is shown to fit several diverse scaffolds.

Carbon Nanoparticles

1,3-Dipolar cycloadditions of Stone–Wales defective single-walled carbon nanotubes: A theoretical study

Tao Yang ,Xiang Zhao [Xi'an Jiaotong University], Shigeru Nagase

J. Comp. Chem., **34**, 2223–2232, 2013.

The presence of Stone-Wales defects in single-walled carbon nanotubes (SWNTs) not only leads to new interesting properties, but also provides opportunities for tailoring physical and chemical properties, and expands their novel potential applications. With a two-layered ONIOM method, 1,3-dipolar cycloadditions (1,3-DCs) of a series of 1,3-dipoles (azomethine ylide, nitrone, nitrile imine, nitrile ylide, nitrile oxide, and methyl azide) with Stone-Wales defective SWNTs have been investigated theoretically for the first time.

Revised Basin-Hopping Monte Carlo Algorithm for Structure Optimization of Clusters and Nanoparticles

Gustavo G. Rondina [Universidade de São Paulo] and Juarez L. F. Da Silva

J.Chem. Infor. and Mod. **53**, 2282–2298, 2013.

Suggestions for improving the Basin-Hopping Monte Carlo (BHMC) algorithm for unbiased global optimization of clusters and nanoparticles are presented. The traditional basin-hopping exploration scheme with Monte Carlo sampling is improved by bringing together novel strategies and techniques employed in different global optimization methods, however, with the care of keeping the underlying algorithm of BHMC unchanged. The improvements include a total of eleven local and nonlocal trial operators tailored for clusters and nanoparticles that allow an efficient exploration of the potential energy surface, two different strategies (static and dynamic) of operator selection, and a filter operator to handle unphysical solutions.

Vibrating-Charge-Driven Water Pump Controlled by the Deformation of the Carbon Nanotube

Xiaoyan Zhou, Fengmin Wu, Jianlong Kou, Xuanchuan Nie, Yang Liu, and Hangjun Lu [Zhejiang Normal University]

J. Phys. Chem. B., **117**, 11681–11686, 2013**.**

The directed transport of water molecules in a single-walled carbon nanotube (SWNT) based on a ratchet effect is investigated by molecular dynamics simulations. The system is driven far away from thermal equilibrium by an additional deterministic perturbation of a vibrating charge, and the spatial inversion symmetry is broken by the continuous deformations of the SWNT. It is well-known that the water flux across a circular channel decreases when the channel is narrowed or deformed.

Interaction of Pristine and Functionalized Carbon Nanotubes with Lipid Membranes

Svetlana Baoukina, Luca Monticelli, and D. Peter Tieleman [University of Calgary]

J. Phys. Chem. B., **117**, 12113–12123, 2013**.**

Carbon nanotubes are widely used in a growing number of applications. Their interactions with biological materials, cell membranes in particular, is of interest in applications including drug delivery and for understanding the toxicity of carbon nanotubes. We use extensive molecular dynamics simulations with the MARTINI model to study the interactions of model nanotubes of different thickness, length, and patterns of chemical modification with model membranes. In addition, we characterize the interactions of small bundles of carbon nanotubes with membrane models. Short pristine carbon nanotubes readily insert into membranes and adopt an orientation parallel to the plane of the membrane in the center of the membrane.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

eSBMTools 1.0: enhanced native structure-based modeling tools

Benjamin Lutz, Claude Sinner, Geertje Heuermann, Abhinav Verma, Alexander Schug[Karlsruhe Institute of Technology]

Bioinformatics. **29,** 2795-2796, 2013.

eSBMTools streamlines running and evaluating SBM in a comprehensive package and offers high flexibility in adding experimental- or bioinformatics-derived restraints. We present a software package that allows setting up, modifying and evaluating SBM for both RNA and proteins. The implemented workflows include predicting protein complexes based on bioinformatics-derived inter-protein contact information, a standardized setup of protein folding simulations based on the common PDB format, calculating reaction coordinates and evaluating the simulation by free-energy calculations.

Computational Design of an Unnatural Amino Acid Dependent Metalloprotein with Atomic Level Accuracy

Jeremy H. Mills, Sagar D. Khare, Jill M. Bolduc, Farhad Forouhar, Vikram Khipple Mulligan, Scott Lew, Jayaraman Seetharaman, Liang Tong, Barry L. Stoddard, and David Baker [University of Washington]

J. Am. Chem. Soc., 2013, **135**, 13393–13399

Computational design methods have been used to identify optimal locations for functional sites in proteins and design the surrounding residues but have not incorporated unnatural amino acids in this process. We extended the Rosetta design methodology to design metalloproteins in which the amino acid (2,2′-bipyridin-5yl)alanine (Bpy-Ala) is a primary ligand of a bound metal ion. Following initial results that indicated the importance of buttressing the Bpy-Ala amino acid, we designed a buried metal binding site with octahedral coordination geometry consisting of Bpy-Ala, two protein-based metal ligands, and two metal-bound water molecules.

LIBEFP: A new parallel implementation of the effective fragment potential method as a portable software library

Ilya A. Kaliman[Purdue University], Lyudmila V. Slipchenko

J. Comp. Chem., **34**, 2284–2292, 2013.

A new high performance parallel implementation of the general Effective Fragment Potential (EFP) method in a form of a portable software library called *libefp* is presented. The *libefp* library was designed to provide developers of various quantum chemistry software packages with an easy way to add EFP functionality to the program of their choice. The general overview of the library is presented and various aspects of interfacing the library with third party quantum chemistry packages are considered.

Computational protein design: The proteus software and selected applications

Thomas Simonson Ecole Polytechnique, Palaiseau], Thomas Gaillard,David Mignon, Marcel Schmidt am Busch, Anne Lopes, Najette Amara,Savvas Polydorides, Audrey Sedano,Karen Druar, Georgios Archontis

J. Comp. Chem., **34**, 2472–2484, 2013.

A!

We describe an automated procedure for protein design, implemented in a flexible software package, called Proteus. System setup and calculation of an energy matrix are done with the XPLOR modeling program and its sophisticated command language, supporting several force fields and solvent models. A second program provides algorithms to search sequence space. It allows a decomposition of the system into groups, which can be combined in different ways in the energy function, for both positive and negative design.

Bioinformatics and Cheminformatics (Cont'd)

Discovery of Most Stable Structures of Neutral and Anionic Phenylalanine through Automated Scanning of Tautomeric and Conformational Spaces

Zibo G. Keolopile [Heriot-Watt University], Maciej Gutowski, and Maciej Haranczyk

J. Chem. Theor. and Comp, **9**, 4374–4381, 2013.

We have developed a software tool for combinatorial generation of tautomers and conformers of small molecules. We have demonstrated it by performing a systematic search for the most stable structures of neutral and anionic phenylalanine (Phe) using electronic structure methods. For the neutral canonical tautomer we found out that the conformers*with* and *without* the intramolecular (O)H···NH_2 hydrogen bond are similarly stable, within the error bars of our method. A unique IR signature of the conformer without the hydrogen bond has been identified. We also considered anions of Phe, both valence type and dipole-bound.

Optimization of 3D Poisson–Nernst-Planck model for fast evaluation of diverse protein channels

Witold Dyrka, Maciej M. Bartuzel and Malgorzata Kotulska

Proteins: Stru. Fun. & Bioinf., **81**, 1802–1822, 2013.

Due to its high computational efficiency, our model can predict the full current-voltage characteristics of a channel within minutes, based on the experimental 3D structure of the channel or its computational model structure. Compared with other methods, such as Brownian dynamics, which currently needs a few weeks of the computational time, or even much more demanding molecular dynamics modeling, 3D-PNP is the only available method for a function-based evaluation of very numerous tentative structural channel models.

Adaptive Smith–Waterman residue match seeding for protein structural alignment

Christopher M. Topham, Mickaël Rouquier, Nathalie Tarrat,Isabelle André [Université de Toulouse]

Proteins: Stru. Fun. & Bioinf., **81**, 1823–1839, 2013.

The POLYFIT rigid-body algorithm for automated global pairwise and multiple protein structural alignment is presented. Smith–Waterman local alignment is used to establish a set of seed equivalences that are extended using Needleman–Wunsch dynamic programming techniques. Structural and functional interaction constraints provided by evolution are encoded as one-dimensional residue physical environment strings for alignment of highly structurally overlapped protein pairs.

A!

DNABind: A hybrid algorithm for structure-based prediction of DNA-binding residues by combining machine learning- and template-based approaches

Rong Liu and Jianjun Hu [University of South Carolina]

Proteins: Stru. Fun. & Bioinf., **81**, 1885–1899, 2013.

Accurate prediction of DNA-binding residues has become a problem of increasing importance in structural bioinformatics. Here, we presented DNABind, a novel hybrid algorithm for identifying these crucial residues by exploiting the complementarity between machine learning- and template-based methods. Our machine learning-based method was based on the probabilistic combination of a structure-based and a sequence-based predictor, both of which were implemented using support vector machines algorithms.

S!

Protein Confirmational Analysis

Improvement of the Treatment of Loop Structures in the UNRES Force Field by Inclusion of Coupling between Backbone- and Side-Chain-Local Conformational States

Paweł Krupa, Adam K. Sieradzan[University of Gdańsk], S. Rackovsky, Maciej Baranowski, Stanisław Ołdziej, Harold A. Scheraga, Adam Liwo, and Cezary Czaplewski

J. Chem. Theor. and Comp, **9**, 4620–4632, 2013.

The UNited RESidue (UNRES) coarse-grained model of polypeptide chains, developed in our laboratory, enables us to carry out millisecond-scale molecular-dynamics simulations of large proteins effectively. It performs well in *ab initio* predictions of protein structure, as demonstrated in the last Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction (CASP10). However, the resolution of the simulated structure is too coarse, especially in loop regions, which results from insufficient specificity of the model of local interactions.

Molecular modeling studies give hint for the existence of a symmetric hβ$_2$R-Gαβγ-homodimer

Andrea Straßer [University of Regensburg], Hans-Joachim Wittmann

J. Mol.Mod., **19,** 4443-4457, 2013.

Several experimental studies suggest that GPCR dimers or oligomers may play an important role in signal transduction. In 2011 the crystal structure of a hβ$_2$R-Gαβγ-complex was published and crystal structures of GPCR dimers are known. But until now, no crystal structure of a GPCR dimer including the Gαβγ-complex is available. In order to obtain detailed insights into interactions within hβ$_2$R dimers including the Gαβγ-complex we performed a potential-energy-surface scan in order to identify favored asymmetric and symmetric hβ$_2$R-Gαβγ-homodimers.

Insight into α-Synuclein Plasticity and Misfolding from Differential Micelle Binding

Parichita Mazumder, Jae-Eun Suk, and Tobias S. Ulmer [University of Southern California]

J. Phys. Chem. B., **117**, 11448-11459, 2013**.**

Misfolded species of the 140-residue protein α-synuclein (αS) are implicated in the demise of dopaminergic neurons, resulting in fatal neurodegeneration. The intrinsically unstructured protein binds curved synaptic vesicle membranes in helical conformations but misfolds into amyloid fibrils via β-sheet interactions. Breaks in helical αS conformation may offer a pathway to transition from helical to sheet conformation. Here, we explore the evolution of broken αS helix conformations formed in complex with SDS and SLAS micelles by molecular dynamics simulations.

Familial Alzheimer's Disease Osaka Mutant (ΔE22) β-Barrels Suggest an Explanation for the Different Aβ$_{1–40/42}$ Preferred Conformational States Observed by Experiment

Hyunbum Jang, Fernando Teran Arce, Srinivasan Ramachandran, Bruce L. Kagan, Ratnesh Lal, and Ruth Nussinov [National Cancer Institute]

J. Phys. Chem. B., **117**, 11518–11529, 2013**.**

An unusual ΔE693 mutation in the amyloid precursor protein (APP) producing a β-amyloid (Aβ) peptide lacking glutamic acid at position 22 (Glu22) was recently discovered, and dabbed the Osaka mutant (ΔE22). Previously, several point mutations in the Aβ peptide involving Glu22 substitutions were identified and implicated in the early onset of familial Alzheimer's disease (FAD). To see whether this aggregation-prone Aβ mutant could directly relate to the Aβ ion channel-mediated mechanism as observed for the wild type (WT) Aβ peptide in AD pathology, we modeled Osaka mutant β-barrels in a lipid bilayer.

Protein Confirmational Analysis (Cont'd)

Molecular Dynamics Simulations of Human Serum Albumin and Role of Disulfide Bonds

Maria Monica Castellanos and Coray M. Colina[The Pennsylvania State University]

J. Phys. Chem. B., **117**, 11895-11905, 2013**.**

Atomistic molecular dynamics simulations of human serum albumin in the presence and absence of disulfide bonds are presented. Simulations of 70 ns duration provide information on the relevance of disulfide bonds in the dynamics and structural conformation of HSA. Significant conformational changes are observed in the absence of disulfide bonds after 35 ns that could impact the functionality and stability of the protein. Changes in the secondary structure, hydrogen bonds, *B* factors, and cross-correlations reveal which disulfide bonds are important for keeping the secondary and tertiary structure and dynamics of the protein and which have little effect on the local structure and dynamics.

Revealing Hidden Helix Propensity in Aβ Peptides by Molecular Dynamics Simulations

Christopher Lockhart and Dmitri K. Klimov[George Mason University]

J. Phys. Chem. B., **117**, 12030–12038, 2013**.**

Using all-atom explicit solvent model and exhaustive replica exchange molecular dynamics simulations we studied the conformational ensembles of several amino-truncated Aβ peptides. In our simulations we specifically monitored the formation of helix structure in the C-terminals of various Aβ fragments. We show that the equilibrium distributions of structures adopted by Aβ23–40 and Aβ10–40 are similar, but sharply distinct from the conformational ensemble of Aβ29–40. The latter features a stable helical structure not present in longer fragments.

Protein Structure Analysis

Identifying protein complexes from heterogeneous biological data

Min Wu [Institute for Infocomm Research, A*STAR], Zhipeng Xie, Xiaoli Li, Chee-Keong Kwoh and Jie Zheng

Proteins: Stru. Fun. & Bioinf., **81**, 2023–2033, 2013.

With the increasing availability of diverse biological information for proteins, integration of heterogeneous data becomes more useful for many problems in proteomics, such as annotating protein functions, predicting novel protein–protein interactions and so on. In this paper, we present an integrative approach called InteHC (Integrative Hierarchical Clustering) to identify protein complexes from multiple data sources. Although integrating multiple sources could effectively improve the coverage of current insufficient protein interactome (the false negative issue), it could also introduce potential false-positive interactions that could hurt the performance of protein complex prediction.

Protein Dynamics

Proline Substitution of Dimer Interface β-strand Residues as a Strategy for the Design of Functional Monomeric Proteins

Prem Raj B. Joseph,Krishna Mohan Poluri,Pavani Gangavarapu,Lavanya Rajagopalan, Sandeep Raghuwanshi,Ricardo M. Richardson, Roberto P. Garofalo,Krishna Rajarathnam[The University of Texas Medical Branch]

Biophysical Journal. **105**, 1491-1501, 2013.

Proteins that exist in monomer-dimer equilibrium can be found in all organisms ranging from bacteria to humans; this facilitates fine-tuning of activities from signaling to catalysis. However, studying the structural basis of monomer function that naturally exists in monomer-dimer equilibrium is challenging. In this study, we show that disrupting backbone H-bonding interactions by substituting dimer interface β-strand residues with proline (Pro) results in fully folded and functional monomers, by exploiting proline's unique feature, the lack of a backbone amide proton.

Molecular dynamics simulations of retinoblastoma protein

C. Ramakrishnan, V. Subramanian, K. Balamurugan & D. Velmurugan[University of Madras]

*J. Biomol. Stru. and Dyn., **31**(11),* 1277-1292, *2013.*

Retinoblastoma protein (pRB) is one among them which regulates G1-S transition by binding with transcription factors. The activity of pRB is deregulated by cyclin dependent kinases-mediated hyper-phosphorylation and also due to cancer-derived mutations. In addition, it is also deactivated by binding of viral onco-proteins such as large T antigen, E1A, and E7. These viral proteins initially recognize pRB through their conserved LxCxE motif and facilitate dissociation of preexisting pRB–E2F complex. Based on these features, molecular dynamics (MD) simulation is performed for four different states of pRB for which the crystal structure is available.

Molecular Dynamics Simulations of Highly Crowded Amino Acid Solutions: Comparisons of Eight Different Force Field Combinations with Experiment and with Each Other

Casey T. Andrews and Adrian H. Elcock [University of Iowa]

J. Chem. Theor. and Comp, **9**, 4585–4602, 2013.

Although it is now commonly accepted that the highly crowded conditions encountered inside biological cells have the potential to significantly alter the thermodynamic properties of biomolecules, it is not known to what extent the thermodynamics of fundamental types of interactions such as salt bridges and hydrophobic interactions are strengthened or weakened by high biomolecular concentrations. As one way of addressing this question we have performed a series of all-atom explicit solvent molecular dynamics (MD) simulations to investigate the effect of increasing solute concentration on the behavior of four types of zwitterionic amino acids in aqueous solution.

Protein Dynamics (Cont'd)

Molecular Dynamics Perspective on the Protein Thermal Stability: A Case Study Using SAICAR Synthetase

Kavyashree Manjunath and Kanagaraj Sekar [Indian Institute of Science]

J.Chem. Infor. and Mod. **53**, 2448–2461, 2013.

S!

The enzyme SAICAR synthetase ligates aspartate with CAIR (5′-phosphoribosyl-4-carboxy-5-aminoimidazole) forming SAICAR (5-amino-4-imidazole-N-succinocarboxamide ribonucleotide) in the presence of ATP. In continuation with our previous study on the thermostability of this enzyme in hyper-/thermophiles based on the structural aspects, here, we present the dynamic aspects that differentiate the mesophilic (*E. coli*, *E. chaffeensis*), thermophilic (*G. kaustophilus*), and hyperthermophilic (*M. jannaschii*, *P. horikoshii*) SAICAR synthetases by carrying out a total of 11 simulations.

Molecular dynamics study of Na^+transportation in a cyclic peptide nanotube and its influences on water behaviors in the tube

Xuezeng Song,Jianfen Fan [Soochow University], Dongyan Liu, Hui Li, Rui Li

J. Mol.Mod., **19,** 4271-4282, 2013.

The dynamics of Na^+ transportation in a transmembrane cyclic peptide nanotube of $8 \times (WL)_4$/POPE has been simulated. The curve of PMF (potential of mean force) for Na^+ moving through the tube, based on ABF (adaptive biasing force) method, indicates that Na^+ possesses lower free energy in an α-plane region than in a mid-plane one. It was found that Na^+ would desorb one or two water molecules in the first solvation shell when entering the tube and later maintain in a solvation state.

Aggregation of Oligoarginines at Phospholipid Membranes: Molecular Dynamics Simulations, Time-Dependent Fluorescence Shift, and Biomimetic Colorimetric Assays

Mario Vazdar [Rudjer Bošković Institute], Erik Wernersson, Morteza Khabiri, Lukasz Cwiklik, Piotr Jurkiewicz, Martin Hof, Ella Mann, Sofiya Kolusheva, Raz Jelinek, and Pavel Jungwirth

J. Phys. Chem. B., **117**, 11530–11540, 2013**.**

A time-dependent fluorescence shift method, biomimetic colorimetric assays, and molecular dynamics simulations have been performed in search of explanations why arginine rich peptides with intermediate lengths of about 10 amino acids translocate well through cellular membranes, while analogous lysine rich peptides do not. First, we demonstrate that an important factor for efficient peptide adsorption, as the first prerequisite for translocation across the membrane, is the presence of negatively charged phospholipids in the bilayer. Second, we observe a strong tendency of adsorbed arginine (but not lysine) containing peptides to aggregate at the bilayer surface.

Effects of Hypoxanthine Substitution in Peptide Nucleic Acids Targeting *KRAS2* Oncogenic mRNA Molecules: Theory and Experiment

Jeffrey M. Sanders, Matthew E. Wampole, Chang-Po Chen, Dalip Sethi, Amrita Singh, François-Yves Dupradeau, Fan Wang, Brian D. Gray, Mathew L. Thakur, and Eric Wickstrom [University, Philadelphia]

J. Phys. Chem. B., **117**, 11584-11595, 2013**.**

Genetic disorders can arise from single base substitutions in a single gene. A single base substitution for wild type guanine in the twelfth codon of *KRAS2* mRNA occurs frequently to initiate lung, pancreatic, and colon cancer. We have observed single base mismatch specificity in radioimaging of mutant *KRAS2* mRNA in tumors in mice by *in vivo* hybridization with radiolabeled peptide nucleic acid (PNA) dodecamers. We hypothesized that multimutant specificity could be achieved with a PNA dodecamer incorporating hypoxanthine, which can form Watson–Crick base pairs with adenine, cytosine, thymine, and uracil.

Protein Dynamics (Cont'd)

Excited State Structures and Decay Dynamics of 1,3-Dimethyluracils in Solutions: Resonance Raman and Quantum Mechanical Calculation Study

Ming-Juan Li, Ming-Xia Liu, Yan-Ying Zhao, Ke-Mei Pei, Hui-Gang Wang, and Xuming Zheng [Zhejiang Sci-Tech University], Wei Hai Fang

J. Phys. Chem. B., **117**, 11660–11669, 2013**.**

The resonance Raman spectroscopic study of the excited state structural dynamics of 1,3-dimethyluracil (DMU), 5-bromo-1,3-dimethyluracil (5BrDMU), uracil, and thymine in water and acetonitrile were reported. Density functional theory calculations were carried out to help elucidate the ultraviolet electronic transitions associated with the A-, and B-band absorptions and the vibrational assignments of the resonance Raman spectra. The effect of the methylation at N1, N3 and C5 sites of pyrimidine ring on the structural dynamics of uracils in different solvents were explored on the basis of the resonance Raman intensity patterns.

Why Do Arginine and Lysine Organize Lipids Differently? Insights from Coarse-Grained and Atomistic Simulations

Zhe Wu, Qiang Cui, and Arun Yethiraj [University Avenue]

J. Phys. Chem. B., **117**, 12145–12156, 2013**.**

Here we show that simulations with the coarse-grained (CG) BMW-MARTINI model reproduce the experimental results. An analysis using atomistic and CG models reveals that electrostatic and glycerol–peptide interactions play a crucial role in determining the phase behavior of peptide–lipid mixtures, with the difference between Arg and Lys arising from the stronger interactions of the former with lipid glycerols. In other words, the multivalent nature of the guanidinium group allows Arg to simultaneously interact with both phosphate and glycerol groups, while Lys engages solely with phosphate; this feature of amino acid/lipid interactions has not been emphasized in previous studies.

Molecular Basis of Binding and Stability of Curcumin in Diamide-Linked γ-Cyclodextrin Dimers

Samuel J. Wallace, Tak W. Kee, and David M. Huang [The University of Adelaide]

J. Phys. Chem. B., **117**, 12375–12382, 2013**.**

Curcumin is a naturally occurring molecule with medicinal properties that is unstable in water, whose efficacy as a drug can potentially be enhanced by encapsulation inside a host molecule. In this work, the thermodynamics and mechanism of binding of curcumin to succinamide- and urea-linked γ-cyclodextrin (γ-CD) dimers in water are investigated by molecular dynamics simulations. The simulated binding constants of curcumin to succinamide- and urea-linked γ-CD dimers at 310 K are $11.3 \times 10^6\ M^{-1}$ and $1.6 \times 10^6\ M^{-1}$, respectively, matching well with previous experimental results of $8.7 \times 10^6\ M^{-1}$ and $2.0 \times 10^6 M^{-1}$.

Amino Acid Capture by Aqueous Interfaces. Implications for Biological Uptake

Marilia T. C. Martins-Costa and Manuel F. Ruiz-Lopez [University of Lorraine]

J. Phys. Chem. B., **117**, 12469–12474, 2013**.**

The interactions of natural amino acids with water–hydrophobic interfaces are central to the control of key biological processes, such as passive transport, and to the overall structure and stability of membrane proteins. The study has been carried out by means of Born–Oppenheimer molecular dynamics simulations focusing on the role that the hydrophobicity of the side chain has on the phase transfer mechanism of the amino acid.

Protein Dynamics (Cont'd)

The conserved Arg241-Glu439 salt bridge determines flexibility of the inositol 1,4,5-trisphosphate receptor binding core in the ligand-free state

Yoichi Ida, Akinori Kidera[Yokohama City University]

Proteins: Stru. Fun. & Bioinf., **81**, 1699–1708, 2013.

Inositol 1,4,5-trisphosphate receptor ($InsP_3R$) is an intracellular Ca^{2+}-release channel activated by binding of inositol 1,4,5-trisphosphate ($InsP_3$) to the $InsP_3$ binding core (IBC). Structural change in the IBC upon $InsP_3$ binding is the key process in channel pore opening. In this study, we performed molecular dynamics (MD) simulations of the $InsP_3$-free form of the IBC, starting with removal of $InsP_3$ from the $InsP_3$-bound crystal structure, and obtained the structural ensemble of the $InsP_3$-free form of the IBC.

Impact of the K24N mutation on the transactivation domain of p53 and its binding to murine double-minute clone 2

Yingqian Ada Zhan, Hongwei Wu, Anne T. Powell, Gary W. Daughdrill and F. Marty Ytreberg[University of Idaho]

Proteins: Stru. Fun. & Bioinf., **81**, 1738–1747, 2013.

The level of the p53 transcription factor is negatively regulated by the E3 ubiquitin ligase murine double-minute clone 2 (MDM2). In this study, we have investigated how the K24N mutation affects the affinity, structure, and dynamics of p53TAD binding to MDM2. Nuclear magnetic resonance studies of p53TAD show that the K24N mutant is more flexible and has less transient helical secondary structure than the wild type. Isothermal titration calorimetry measurements demonstrate that these changes in structure and dynamics do not significantly change the binding affinity for p53TAD–MDM2.

The interplay of structure and dynamics: Insights from a survey of HIV-1 reverse transcriptase crystal structures

James M. Seckler, Nicholas Leioatts, Hongyu Miao and Alan Grossfield [University of Rochester]

Proteins: Stru. Fun. & Bioinf., **81**, 1792–1801, 2013.

HIV-1 reverse transcriptase (RT) is a critical drug target for HIV treatment, and understanding the exact mechanisms of its function and inhibition would significantly accelerate the development of new anti-HIV drugs. It is well known that structure plays a critical role in protein function, but for RT, structural information has proven to be insufficient—despite enormous effort—to explain the mechanism of inhibition and drug resistance of non-nucleoside RT inhibitors. We hypothesize that the missing link is dynamics, information about the motions of the system.

Free Energy Calculations

Absolute Free Energy of Binding and Entropy of the FKBP12-FK506 Complex: Effects of the Force Field

Ignacio J. General and Hagai Meirovitch [Bar-Ilan University]

J. Chem. Theor. and Comp, **9**, 4609–4619, 2013.

The hypothetical scanning molecular dynamics (HSMD) method combined with thermodynamic integration (HSMD-TI) has been extended recently for calculating ΔA^0—the absolute free energy of binding of a ligand to a protein. With HSMD-TI, ΔA^0 is obtained in a new way as a sum of several components, among them is ΔS_{ligand}—the change in the conformational entropy as the ligand is transferred from the bulk solvent to the active site—this entropy is obtained by a specific reconstruction procedure.

Free Energy Calculations (Cont'd)

Free Energy Surface for Brønsted Acid-Catalyzed Glucose Ring-Opening in Aqueous Solution

Xianghong Qian [University of Arkansas]

J. Phys. Chem. B., **117**, 11460–11465, 2013**.**

Car–Parrinello-based molecular dynamics coupled with metadynamics simulations were used to determine the mechanism and associated free energy surface for opening the ring structure of cyclic glucopyranose in acidic aqueous solutions. The ring-opening process is initiated by the protonation of the ring oxygen atom and the breakage of the C1–O5 bond. The barrier for this process is about 25 kcal/mol, in good agreement with experimental measurements.

Ligand Binding/Docking

Effects of ATP and Actin-Filament Binding on the Dynamics of the Myosin II S1 Domain

Joseph L. Baker, Gregory A. Voth[University of Chicago]

Biophysical Journal. **105**, 1624-1634, 2013.

Using all-atom level and coarse-grained analysis methods, we investigate the effects of myosin binding on actin, and of actin binding on myosin. In particular, we determine the domains of actin and myosin that interact strongly with one another at the actomyosin interface using a highly coarse-grained level of resolution, and we identify a number of salt bridges and hydrogen bonds at the interface of myosin and actin. Applying coarse-grained analysis, we identify differences in myosin states dependent on actin-binding, or ATP binding.

Probing the Flexibility of Tropomyosin and Its Binding to Filamentous Actin Using Molecular Dynamics Simulations

Wenjun Zheng [University at Buffalo], Bipasha Barua, Sarah E. Hitchcock-DeGregori

Biophysical Journal. **105**, 1882-1892, 2013.

Based on the simulations, we systematically analyzed the local flexibility of the Tm coiled coil using multiple parameters. We found a good correlation between the regions with high local flexibility and a number of destabilizing regions in Tm, including six clusters of core alanines. Despite the stabilization by F-actin binding, the distribution of local flexibility in Tm is largely unchanged in the absence and presence of F-actin. Our simulations showed variable fluctuations of individual Tm periods from the closed position toward the open position.

Mechanism of Transient Binding and Release of Substrate Protein during the Allosteric Cycle of the p97 Nanomachine

Sam Tonddast-Navaei and George Stan [University of Cincinnati]

J. Am. Chem. Soc., 2013, **135**, 14627–14636

We use molecular dynamics simulations to probe the interaction between p97 and an extended peptide substrate. Mechanical pulling of the substrate through the p97 pore reveals that smaller work is required for translocation from the D1 toward the D2 compartment than in the opposite direction. These distinct energetic requirements originate in structural aspects and chemical properties of the pore lining. Whereas van der Waals interactions are dominant within the D1 pore, interaction within the D2 pore are strongly electrostatic.

Ligand Binding / Docking (Cont'd)

Computational Analysis of the Binding Specificity of Gleevec to Abl, c-Kit, Lck, and c-Src Tyrosine Kinases

Yen-Lin Lin and Benoît Roux [The University of Chicago]

J. Am. Chem. Soc., 2013, **135**, 14741–14753

Gleevec, a well-known cancer therapeutic agent, is an effective inhibitor of several tyrosine kinases, including Abl and c-Kit, but displays less potency to inhibit closely homologous tyrosine kinases, such as Lck and c-Src. Because many structural features of the binding site are highly conserved in these homologous kinases, the molecular determinants responsible for the binding specificity of Gleevec remain poorly understood. To address this issue, free energy perturbation molecular dynamics (FEP/MD) simulations with explicit solvent was used to compute the binding affinity of Gleevec to Abl, c-Kit, Lck, and c-Src.

The 'order-to-disorder' conformational transition in CD44 protein: An umbrella sampling analysis

Wojciech Plazinski [J. Haber Institute of Catalysis and Surface Chemistry] , Agnieszka Knys-Dzieciuch

J. Mol.Graph. and Mod., **45,** 122-127, 2013.

The molecule of CD44, a membrane protein being the major cell surface receptor for hyaluronan, is postulated to undergo the conformational rearrangement called the 'order-to-disorder' transition. The experimental studies suggest that the Tyr161 residue is crucial for maintaining the equilibrium between the 'ordered' (O) and 'partially disordered' (PD) forms of CD44. The molecular modeling study based on the umbrella sampling protocol was carried out separately for the wild-type CD44 and Tyr161Ala mutant in order to gain more insight into the molecular mechanism of the O-PD transition and to clarify the role of the Tyr161 amino acid residue.

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hERG Me Out

Paul Czodrowski [Global Computational Chemistry]

J.Chem. Infor. and Mod. **53**, 2240-2251, 2013.

S!

A detailed analysis of the hERG content inside the ChEMBL database is performed. The correlation between the outcome from binding assays and functional assays is probed. On the basis of descriptor distributions, design paradigms with respect to structural and physicochemical properties of hERG active and hERG inactive compounds are challenged. Finally, classification models with different data sets are trained.

Ligand binding and dynamics of the monomeric epidermal growth factor receptor ectodomain

Hannes H. Loeffler and Martyn D. Winn [Scientific Computing Department, STFC Daresbury]

Proteins: Stru. Fun. & Bioinf., **81**, 1931–1943, 2013.

The ectodomain of the human epidermal growth factor receptor (hEGFR) controls input to several cell signalling networks via binding with extracellular growth factors. To gain insight into the dynamics and ligand binding of the ectodomain, the hEGFR monomer was subjected to molecular dynamics simulation. The monomer was found to be substantially more flexible than the ectodomain dimer studied previously. Simulations where the endogeneous ligand EGF binds to either Subdomain I or Subdomain III, or where hEGFR is unbound, show significant differences in dynamics.

Enzyme Catalysis

Amine Oxidation Mediated by Lysine-Specific Demethylase 1: Quantum Mechanics/Molecular Mechanics Insights into Mechanism and Role of Lysine 661

Bora Karasulu, Mahendra Patil, and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Am. Chem. Soc., 2013, **135**, 13400–13413

We report classical molecular dynamics (MD) simulations and combined quantum mechanics/molecular mechanics (QM/MM) calculations to elucidate the catalytic mechanism of the rate-determining amine oxidation step in the lysine-specific demethylase 1 (LSD1)-catalyzed demethylation of the histone tail lysine (H3K4), with flavin adenine dinucleotide (FAD) acting as cofactor. The oxidation of substrate lysine (sLys) involves the cleavage of an α-CH bond accompanied by the transfer of a hydride ion equivalent to FAD, leading to an imine intermediate.

Phosphoryl Transfers of the Phospholipase D Superfamily: A Quantum Mechanical Theoretical Study

Nathan J. DeYonker and Charles Edwin Webster [The University of Memphis]

J. Am. Chem. Soc., 2013, **135**, 13764-13774

The HKD-containing Phospholipase D superfamily catalyzes the cleavage of the headgroup of phosphatidylcholine to produce phosphatidic acid and choline. The mechanism of this cleavage process is studied theoretically. The geometric basis of our models is the X-ray crystal structure of the five-coordinate phosphohistidine intermediate from *Streptomyces sp*. Strain PMF (PDB Code = 1V0Y). Hybrid ONIOM QM:QM methodology with DFT and semiempirical PM6 is used to acquire thermodynamic and kinetic data for the initial phosphoryl transfer, subsequent hydrolysis, and finally, the formation of the experimentally observed ″dead-end″ phosphohistidine.

Mechanism of Acyl–Enzyme Complex Formation from the Henry–Michaelis Complex of Class C β-Lactamases with β-Lactam Antibiotics

Ravi Tripathi and Nisanth N. Nair [Indian Institute of Technology Kanpur]

J. Am. Chem. Soc., 2013, **135**, 114679–14690

Bacteria that cause most of the hospital-acquired infections make use of class C β-lactamase (CBL) among other enzymes to resist a wide spectrum of modern antibiotics and pose a major public health concern. We carried out extensive hybrid quantum mechanical/molecular mechanical Car–Parrinello molecular dynamics simulation of the reaction with the aid of the metadynamics technique. On this basis, we report here the mechanism of the formation of the acyl–enzyme complex from the Henry–Michaelis complex formed by β-lactam antibiotics and CBL.

Methyl-Coenzyme M Reductase from Methanogenic Archaea: Isotope Effects on Label Exchange and Ethane Formation with the Homologous Substrate Ethyl-Coenzyme M

Silvan Scheller, Meike Goenrich, Rudolf K. Thauer, and Bernhard Jaun [Laboratory of Organic Chemistry, ETH Zurich]

J. Am. Chem. Soc., 2013, **135**, 14985–14995

Ethyl-coenzyme M (CH_3CH_2-S-CH_2CH_2-SO_3^-, Et-S-CoM) serves as a homologous substrate for the enzyme methyl-coenzyme M reductase (MCR) resulting in the product ethane instead of methane. The catalytic reaction proceeds via an intermediate that already contains all six C–H bonds of the product. In deuterated buffer, the intermediate becomes labeled, and C–H activation in the back reaction rapidly leads to labeled Et-S-CoM, which enables intermediate formation to be detected. Here, we present a comprehensive analysis of this pre-equilibrium.

Enzyme Catalysis (Cont'd)

Ligand release mechanisms and channels in histone deacetylases

Subha Kalyaanamoorthy, Yi-Ping Phoebe Chen [La Trobe University]

J. Comp. Chem., **34**, 2270–2283, 2013.

Exploring the molecular channels of class I histone deacetylases (HDACs) with buried active sites are important to understand their structures and functionalities. In this work, we perform hybrid classical molecular dynamics and random acceleration molecular dynamics simulations to explore the B3N [i.e., (4-(dimethylamino)N-[7(hydroxyamino)-7-oxoheptyle] benzamide)] exit channels in the x-ray crystal structures of HDAC3 and HDAC8 enzymes.

Exploring the effect of PARP-1 flexibility in docking studies

Albert A. Antolin , Andrea Carotti , Roberto Nuti , Aydie Hakkaya ,Emidio Camaioni ,Jordi Mestres ,Roberto Pellicciari ,Antonio Macchiarulo [IMIM Hospital del Mar Research Institute and Universitat Pompeu Fabra]

J. Mol.Graph. and Mod., **45,** 192–201, 2013.

S!

Poly(ADP-ribose)polymerase-1 (PARP-1) is an enzyme belonging to the ADP-ribosyltransferase family. A large body of works has validated PARP-1 as an attractive drug target for different therapeutic areas, including cancers and ischemia. Accordingly, sampling the conformational space of the enzyme is pivotal to understand its functions and improve structure-based drug discovery approaches. In the first part of this study we apply replica exchange molecular dynamic (REMD) simulations to sample the conformational space of the catalytic domain of PARP-1 in the ligand-bound and unbound forms.

Flooding Enzymes: Quantifying the Contributions of Interstitial Water and Cavity Shape to Ligand Binding Using Extended Linear Response Free Energy Calculations

Katie L. Whalen and M. Ashley Spies [The University of Iowa]

J.Chem. Infor. and Mod. **53**, 2349-2359, 2013.

Glutamate racemase (GR) is a cofactor independent amino acid racemase that has recently garnered increasing attention as an antimicrobial drug target. There are numerous high resolution crystal structures of GR, yet these are invariably bound to either D-glutamate or very weakly bound oxygen-based salts. In order to validate key contacts between the buried sulfonate moiety of BISA and moieties in the back of the enzyme active site, as well as to probe the energetic importance of the potentially large number of interstitial waters contacted by the BISA scaffold, we have designed several mutants of Asn75.

Exploring the Desumoylation Process of SENP1: A Study Combined MD Simulations with QM/MM Calculations on SENP1-SUMO1-RanGAP1

Ting Shi, Yuhui Han, Weihua Li, Yanlong Zhao, Yaqin Liu, Zhimin Huang, Shaoyong Lu, and Jian Zhang [Shanghai Jiao-Tong University School of Medicine]

J.Chem. Infor. and Mod. **53**, 2360–2368, 2013.

The small ubiquitin-related modifier (SUMO)-specific protease (SENP) processes SUMOs to mature forms and deconjugates them from various modified substrates. Loss of the equilibrium from desumoylation catalyzed by abnormal SENP1 is associated with cancers and transcription factor activity. In spite of the significant role of SENP1, the molecular basis of its desumoylation remains unclear. Here, MD simulations and QM/MM methods are combined to investigate the catalytic mechanism of desumoylation.

Enzyme Catalysis (Cont'd)

Computational design of a full-length model of HIV-1 integrase: modeling of new inhibitors and comparison of their calculated binding energies with those previously studied

Selami Ercan, Necmettin Pirinccioglu [University of Dicle]

J. Mol.Mod., **19,** 4349-4368, 2013.

A full-length model of integrase (IN) of the human immunodeficiency virus type 1 (HIV-1) was constructed based on the distinctly resolved X-ray crystal structures of its three domains, named N-terminal, catalytic core and C-terminal. Thirty-one already known inhibitors with varieties of structural differences as well as nine newly tested ones were docked into the catalytic core. The molecular dynamic (MD) and binding properties of these complexes were obtained by MD calculations.

Conformation-Directed Catalysis and Coupled Enzyme–Substrate Dynamics in Pin1 Phosphorylation-Dependent Cis–Trans Isomerase

Hector A. Velazquez and Donald Hamelberg[Georgia State University]

J. Phys. Chem. B., **117**, 11509–11517, 2013**.**

Human peptidyl–prolyl cis–trans isomerase NIMA-interacting 1 (Pin1) is an essential enzyme in numerous phosphorylation-dependent regulatory pathways and has been implicated in many diseases. We present results from accelerated MD simulations to show that catalysis occurs along a restricted path of the backbone configuration of the substrate, selecting out specific conformations of the substrate in the active site of Pin1. We show that the dynamics of Pin1 and the enzyme–substrate interactions are intricately coupled to isomerization during catalysis.

Exploring the Possible Role of Glu286 in C*c*O by Electrostatic Energy Computations Combined with Molecular Dynamics

Anna Lena Woelke, Gegham Galstyan, Artur Galstyan, Tim Meyer, Joachim Heberle, and Ernst-Walter Knapp [Freie Universität Berlin]

J. Phys. Chem. B., **117**, 12432-12441, 2013**.**

Cytochrome *c* oxidase (C*c*O) is a central enzyme in aerobic life catalyzing the conversion of molecular oxygen to water and utilizing the chemical energy to pump protons and establish an electrochemical gradient. Despite intense research, it is not understood how C*c*O achieves unidirectional proton transport and avoids short circuiting the proton pump. Within this work, we analyzed the potential role of Glu286 as a proton valve. We performed unconstrained MD simulations of C*c*O with an explicit membrane for up to 80 ns.

Protein-Protein Interactions

HippDB: a database of readily targeted helical protein–protein interactions

Christina M. Bergey, Andrew M. Watkins, Paramjit S. Arora [New York University]

Bioinformatics. **29**, 2806-2807, 2013.

HippDB catalogs every protein–protein interaction whose structure is available in the Protein Data Bank and which exhibits one or more helices at the interface. The Web site accepts queries on variables such as helix length and sequence, and it provides computational alanine scanning and change in solvent-accessible surface area values for every interfacial residue. HippDB is intended to serve as a starting point for structure-based small molecule and peptidomimetic drug development.

Protein Protein Interactions (Cont'd)

Mining the Characteristic Interaction Patterns on Protein–Protein Binding Interfaces

Yan Li, Zhihai Liu, Li Han, Chengke Li, and Renxiao Wang [Macau University of Science and Technology]

J.Chem. Infor. and Mod. **53**, 2437–2447, 2013.

Protein–protein interactions are observed in various biological processes. They are important for understanding the underlying molecular mechanisms and can be potential targets for developing small-molecule regulators of such processes. Previous studies suggest that certain residues on protein–protein binding interfaces are ″hot spots″. As an extension to this concept, we have developed a residue-based method to identify the characteristic interaction patterns (CIPs) on protein–protein binding interfaces, in which each pattern is a cluster of four contacting residues.

Optimizing Electrostatic Field Calculations with the Adaptive Poisson–Boltzmann Solver to Predict Electric Fields at Protein–Protein Interfaces. I. Sampling and Focusing

Andrew W. Ritchie and Lauren J. Webb[The University of Texas at Austin]

J. Phys. Chem. B., **117**, 11473-11489, 2013**.**

Continuum electrostatics methods are commonly used to calculate electrostatic potentials in proteins and at protein–protein interfaces to aid many types of biophysical studies. Despite their ubiquity throughout the biophysical literature, these calculations are difficult to test against experimental data to determine their accuracy and validity. We have calculated the Boltzmann-weighted electrostatic field at the midpoint of a nitrile bond placed at a variety of locations on the surface of the protein RalGDS, both in its monomeric form as well as when docked to four different constructs of the protein Rap, and compared the computation results to vibrational absorption energy measurements of the nitrile oscillator.

Specific and Non-Specific Protein Association in Solution: Computation of Solvent Effects and Prediction of First-Encounter Modes for Efficient Configurational Bias Monte Carlo Simulations

Antonio Cardone, Harish Pant, and Sergio A. Hassan [National Institutes of Health, Bethesda]

J. Phys. Chem. B., **117**, 12360–12374, 2013**.**

Weak and ultraweak protein–protein association play a role in molecular recognition and can drive spontaneous self-assembly and aggregation. Such interactions are difficult to detect experimentally, and are a challenge to the force field and sampling technique. A method is proposed to identify low-population protein–protein binding modes in aqueous solution. The method is designed to identify preferential first-encounter complexes from which the final complex(es) at equilibrium evolve.

Membrane Proteins and Lipid Peptide Interactions

Protein–ligand binding site recognition using complementary binding-specific substructure comparison and sequence profile alignment

Jianyi Yang, Ambrish Roy, Yang Zhang [University of Michigan]

Bioinformatics. **29**, 2588-2595, 2013.

We develop two new methods, one based on binding-specific substructure comparison (TM-SITE) and another on sequence profile alignment (S-SITE), for complementary binding site predictions. The methods are tested on a set of 500 non-redundant proteins harboring 814 natural, drug-like and metal ion molecules. Starting from low-resolution protein structure predictions, the methods successfully recognize >51% of binding residues with average Matthews correlation coefficient (MCC) significantly higher (with P-value $<10^{-9}$ in student t-test) than other state-of-the-art methods, including COFACTOR, FINDSITE and ConCavity.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulations of Homo-oligomeric Bundles Embedded Within a Lipid Bilayer

Thuy Hien T. Nguyen, Zhiwei Liu, Preston B. Moore[University of the Sciences in Philadelphia]

Biophysical Journal. **105**, 1569-1580, 2013.

We investigated homooligomeric helical bundle systems consisting of synthetic α-helices with either the sequence Ac-$(LSLLLSL)_3$-NH_2 (LS2) or Ac-$(LSSLLSL)_3$-NH_2 (LS3). The LS2 and LS3 helical peptides are designed to have amphipathic characteristics that form ion channels in membrane. We simulated bundles containing one to six peptides that were embedded in palmitoyl-oleoyl-phosphatidylcholine (POPC) lipid bilayer and placed between two lamellae of water. We aim to provide a fundamental understanding of how amphipathic helical peptides interact with each other and their dynamical behaviors in different homooligomeric states.

Interactions between Fengycin and Model Bilayers Quantified by Coarse-Grained Molecular Dynamics

Joshua N. Horn, Aaron Cravens, Alan Grossfield[University of Rochester]

Biophysical Journal. **105**, 1612-1623, 2013.

Bacteria, particularly of the genus Bacillus, produce a wide variety of antifungal compounds. They act by affecting the lipid bilayers of fungal membranes, causing curvature-induced strain and eventual permeabilization. One class of these, known as fengycins, has been commercialized for treating agricultural infections and shows some promise as a possible antifungal pharmaceutical. Understanding the mechanism by which fengycins damage lipid bilayers could prove useful to the future development of related antifungal treatments. In this work, we present multi-microsecond-long simulations of fengycin interacting with different lipid bilayer systems.

The Structural Basis of Cholesterol Accessibility in Membranes

Brett N. Olsen, Agata A. Bielska,Tiffany Lee ,Michael D. Daily,Douglas F. Covey,Paul H. Schlesinger, Nathan A. Baker,Daniel S. Ory [Washington University School of Medicine]

Biophysical Journal. **105**, 1838-1847, 2013.

In this study, we use both molecular dynamics simulations and experimental membrane systems to examine the behavior of cholesterol in membrane bilayers. We find that cholesterol depth within the bilayer provides a reasonable structural metric for cholesterol availability and that this is correlated with cholesterol-acceptor binding. Further, the distribution of cholesterol availability in our simulations is continuous rather than divided into distinct available and unavailable pools.

The Membrane Protein LeuT in Micellar Systems: Aggregation Dynamics and Detergent Binding to the S2 Site

George Khelashvili [Weill Cornell Medical College of Cornell University (WCMC)], Michael V. LeVine, Lei Shi, Matthias Quick, Jonathan A. Javitch, and Harel Weinstein

J. Am. Chem. Soc., 2013, **135**, 14266–14275

Structural and functional properties of integral membrane proteins are often studied in detergent micellar environments (proteomicelles), but how such proteomicelles form and organize is not well understood. This makes it difficult to evaluate the relationship between the properties of the proteins measured in such a detergent-solubilized form and under native conditions. To obtain mechanistic information about this relationship for the leucine transporter (LeuT), a prokaryotic homologue of the mammalian neurotransmitter/sodium symporters (NSSs), we studied the properties of proteomicelles formed by *n*-dodecyl-β,D-maltopyranoside (DDM) detergent.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Prediction of Protein–Ligand Binding Structures by Replica-Exchange Umbrella Sampling Simulations: Application to Kinase Systems

Hironori Kokubo[Takeda Pharmaceutical], Toshimasa Tanaka, and Yuko Okamoto

J. Chem. Theor. and Comp, **9**, 4660-4671, 2013.

We have applied our prediction method, which is based on the replica-exchange umbrella sampling for protein–ligand binding structures, to two kinase systems (p38 and JNK3) with two different ligand molecules for each kinase. Starting from configurations in which the protein and the ligand are far away from each other, our method predicted the ligand binding structures in excellent agreement with the experimental data from PDB in all four cases, which suggests the general applicability of our method to kinase systems.

Behavior of Human Cytochromes P450 on Lipid Membranes

Karel Berka, Markéta Paloncýová, Pavel Anzenbacher, and Michal Otyepka [Palacký University Olomouc]

J. Phys. Chem. B., **117**, 11556–11564, 2013**.**

Human cytochromes P450 (CYPs) are membrane-anchored enzymes involved in biotransformation of many marketed drugs. We constructed atomic models of six human CYPs (CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4) anchored to a lipid bilayer to investigate the positions and orientations of CYPs on a membrane. We equilibrated the models by molecular dynamics simulations on a 100+ ns time scale. Catalytic domains of all studied CYPs were found to be partially immersed in the lipid bilayer, whereas the N-terminal part and F′/G′ loop are deeply immersed.

Molecular Dynamics Simulations of Ion Conductance in Field-Stabilized Nanoscale Lipid Electropores

Ming-Chak Ho, Maura Casciola, Zachary A. Levine, and P. Thomas Vernier [University of Southern California]

J. Phys. Chem. B., **117**, 11633–11640, 2013**.**

Molecular dynamics (MD) simulations of electrophoretic transport of monovalent ions through field-stabilized electropores in POPC lipid bilayers permit systematic characterization of the conductive properties of lipid nanopores. We examined pore conductances for two monovalent salts, NaCl and KCl, at physiological concentrations. Na^+ conductance is significantly less than K^+ and Cl^- conductance and is a nonlinear function of pore radius over the range of pore radii investigated. The single pore electrical conductance of KCl obtained from MD simulation is comparable to experimental values measured by chronopotentiometry.

Free Energetics of Arginine Permeation into Model DMPC Lipid Bilayers: Coupling of Effective Counterion Concentration and Lateral Bilayer Dimensions

Yuan Hu, Shuching Ou, and Sandeep Patel [University of Delaware]

J. Phys. Chem. B., **117,**11641–11653, 2013**.**

We use fully atomistic molecular dynamics simulations coupled with the adaptive biasing force (ABF) method for free energy estimation. The estimated potential of mean force difference from bulk to bilayer center is 6.94 ± 0.28 kcal/mol. The order of magnitude of this prediction is consistent with past experimental estimates of arginine partitioning into physiological bilayers in the context of translocon-based experiments, though the correlation between the bench and computer experiments is not unambiguous. Moreover, the present value is roughly one-half of previous estimates based on all-atom molecular dynamics free energy calculations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

The Different Interactions of Lysine and Arginine Side Chains with Lipid Membranes

Libo Li, Igor Vorobyov, and Toby W. Allen [RMIT University]

J. Phys. Chem. B., **117**, 11906-11920, 2013**.**

In this study, we employ fully atomistic molecular dynamics simulations to observe, quantify, and compare the interactions of Lys and Arg with saturated phosphatidylcholine membranes of different thickness. We make use of both charged (methylammonium and methylguanidinium) and neutral (methylamine and methylguanidine) analogue molecules, as well as Lys and Arg side chains on transmembrane helix models. We find that the free energy barrier experienced by a charged Lys crossing the membrane is strikingly similar to that of a charged Arg (to within 2 kcal/mol), despite the two having different chemistries, H-bonding capability, and hydration free energies that differ by ~10 kcal/mol.

Protein Folding

Molecular dynamics simulation of temperature induced unfolding of animal prion protein

Xin Chen[Henan University], Danhui Duan, Shuyan Zhu, Jinglai Zhang

J. Mol.Mod., **19,** 4433-4441, 2013.

To elucidate the structural stability and the unfolding dynamics of the animal prion protein, the temperature induced structural evolution of turtle prion protein (tPrPc) and bank vole prion protein (bvPrPc) have been performed with molecular dynamics (MD) simulation. The unfolding behaviors of secondary structures showed that the α-helix was more stable than β-sheet. Extension and disruption of β-sheet commonly appeared in the temperature induced unfolding process.

Hypothetical in silico model of the early-stage intermediate in protein folding

Barbara Kalinowska, Paweł Alejster, Kinga Sałapa, Zbigniew Baster, Irena Roterman [Jagiellonian University—Medical College]

J. Mol.Mod., **19,** 4259-4269, 2013.

This paper presents a method for determining the structure of the early stage (ES) intermediate in the multistage protein folding process. ES structure is modeled on the basis of a limited conformational subspace of the Ramachandran plot. The model distinguishes seven structural motifs corresponding to seven local probability maxima within the limited conformational subspace. Three of these are assigned to well-defined secondary structures, while the remaining four are found to represent various types of random coils.

Folding Dynamics of the Trp-Cage Miniprotein: Evidence for a Native-Like Intermediate from Combined Time-Resolved Vibrational Spectroscopy and Molecular Dynamics Simulations

Heleen Meuzelaar, Kristen A. Marino, Adriana Huerta-Viga, Matthijs R. Panman, Linde E. J. Smeenk, Albert J. Kettelarij, Jan H. van Maarseveen, Peter Timmerman, Peter G. Bolhuis, and Sander Woutersen[University of Amsterdam]

J. Phys. Chem. B., **117**, 11490–11501, 2013**.**

Trp-cage is a synthetic 20-residue miniprotein which folds rapidly and spontaneously to a well-defined globular structure more typical of larger proteins. Due to its small size and fast folding, it is an ideal model system for experimental and theoretical investigations of protein folding mechanisms. However, Trp-cage's exact folding mechanism is still a matter of debate. Here we investigate Trp-cage's relaxation dynamics in the amide I′ spectral region (1530–1700 cm^{-1}) using time-resolved infrared spectroscopy. Residue-specific information was obtained by incorporating an isotopic label ($^{13}C{=}^{18}O$) into the amide carbonyl group of residue Gly11, thereby spectrally isolating an individual 3_{10}-helical residue.

Protein-Nucleic acid Interactions

Molecular Simulations of Polycation–DNA Binding Exploring the Effect of Peptide Chemistry and Sequence in Nuclear Localization Sequence Based Polycations

Robert M. Elder and Arthi Jayaraman[University of Colorado]

J. Phys. Chem. B., **117**, 11988–11999, 2013**.**

Gene therapy relies on the delivery of DNA into cells, and polycations are one class of vectors enabling efficient DNA delivery. Nuclear localization sequences (NLS), cationic oligopeptides that target molecules for nuclear entry, can be incorporated into polycations to improve their gene delivery efficiency. We use simulations to study the effect of peptide chemistry and sequence on the DNA-binding behavior of NLS-grafted polycations by systematically mutating the residues in the grafts, which are based on the SV40 NLS (peptide sequence PKKKRKV).

Cross-talk between the ligand- and DNA-binding domains of estrogen receptor

Wei Huang, Geoffrey L. Greene, Krishnakumar M. Ravikumar and Sichun Yang [Case Western Reserve University]

Proteins: Stru. Fun. & Bioinf., **81**, 1900–1909, 2013.

Estrogen receptor alpha (ERα) is a hormone-responsive transcription factor that contains several discrete functional domains, including a ligand-binding domain (LBD) and a DNA-binding domain (DBD). Despite a wealth of knowledge about the behaviors of individual domains, the molecular mechanisms of cross-talk between LBD and DBD during signal transduction from hormone to DNA-binding of ERα remain elusive. Here, we apply a multiscale approach combining coarse-grained (CG) and atomistically detailed simulations to characterize this cross-talk mechanism via an investigation of the ERα conformational landscape.

Nucleic Acids

Temperature Dependence of the DNA Double Helix at the Nanoscale: Structure, Elasticity, and Fluctuations

Sam Meyer, Daniel Jost, Nikos Theodorakopoulos , Michel Peyrard, Richard Lavery [University Lyon I/Centre National de la Recherche Scientifique],Ralf Everaers

Biophysical Journal. **105**, 1904-1914, 2013.

Biological organisms exist over a broad temperature range of −15°C to +120°C, where many molecular processes involving DNA depend on the nanoscale properties of the double helix. Here, we present results of extensive molecular dynamics simulations of DNA oligomers at different temperatures. We show that internal basepair conformations are strongly temperature-dependent, particularly in the stretch and opening degrees of freedom whose harmonic fluctuations can be considered the initial steps of the DNA melting pathway. The basepair step elasticity contains a weaker, but detectable, entropic contribution in the roll, tilt, and rise degrees of freedom.

Nucleic Acids (Cont'd)

Cooperative stabilization of Zn^{2+}:DNA complexes through netropsin binding in the minor groove of FdU-substituted DNA

Supratim Ghosh, Freddie R. Salsbury Jr., David A. Horita & William H. Gmeiner[Wake Forest School of Medicine]

J. Biomol. Stru. and Dyn., ***31****(11),* 1301-1310, *2013.*

The simultaneous binding of netropsin in the minor groove and Zn^{2+} in the major groove of a DNA hairpin that includes 10 consecutive FdU nucleotides at the 3′-terminus was demonstrated based upon NMR spectroscopy, circular dichroism (CD), and computational modeling studies. The resulting Zn^{2+}/netropsin: 3′FdU complex had very high thermal stability with aspects of the complex intact at 85 °C, conditions that result in complete dissociation of Mg^{2+}complexes. CD and ^{19}F NMR spectroscopy were consistent with Zn^{2+} binding in the major groove of the DNA duplex.

Effect of initial ion positions on the interactions of monovalent and divalent ions with a DNA duplex as revealed with atomistic molecular dynamics simulations

Timothy J. Robbins & Yongmei Wang [University of Memphis]

J. Biomol. Stru. and Dyn., ***31****(11),* 1311-1323, *2013.*

Different initial placements of ions were tried and the resulting effects on the ion distributions around DNA were investigated. For monovalent ions, results were found to be nearly independent of initial cation coordinates. However, Mg^{2+} ions demonstrated a strong initial coordinate dependent behavior. While some divalent ions initially placed near the DNA formed essentially permanent direct coordination complexes with electronegative DNA atoms, Mg^{2+} ions initially placed further away from the duplex formed a full, nonexchanging, octahedral first solvation shell.

Interaction of Nucleic Acid Bases with the Au(111) Surface

Marta Rosa, Stefano Corni, and Rosa Di Felice [NR Institute of Nanoscience]

J. Chem. Theor. and Comp, **9**, 4552–4561, 2013.

The fate of an individual DNA molecule when it is deposited on a hard inorganic surface in a "dry" environment is unknown, while it is a crucial determinant for nanotechnology applications of nucleic acids. In the absence of experimental approaches that are able to unravel the three-dimensional atomic structure of the target system, here we tackle the first step toward a computational solution of the problem. By using first-principles QM calculations of the four nucleobases on the Au(111) surface, we present results for the geometries, energetics, and electronic structure, in view of developing a force field that will enable classical simulations of DNA on Au(111) to investigate the structural modifications of the duplex in these non-native states.

Effect of 8-Oxoguanine on DNA Structure and Deformability

Tomáš Dršata, Mahmut Kara, Martin Zacharias, and Filip Lankaš [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **117**, 11617–11622, 2013**.**

8-Oxoguanine (oxoG) is an abundant product of oxidative DNA damage. It is removed by repair glycosylases, but exactly how the enzymes recognize oxoG in the large surplus of undamaged bases is not fully understood. The lesion may induce changes in the properties of naked DNA that facilitate the recognition. In this work, we assess the effect of oxoG on DNA structure and mechanical deformability. We performed extensive unrestrained, atomic resolution MD simulations to parametrize a nonlocal, rigid base mechanical model of DNA.

Nucleic Acids (Cont'd)

π- vs σ-Radical States of One-Electron-Oxidized DNA/RNA Bases: A Density Functional Theory Study

Anil Kumar and Michael D. Sevilla [Oakland University]

J. Phys. Chem. B., **117**, 11623–11632, 2013**.**

We used DFT B3LYP/6-31++G** method to optimize the geometries of π- and σ-radicals in C_s symmetry (i.e., planar) in the gas phase and in solution using the polarized continuum model (PCM). The calculations predict that σ- and π-radical states in one-electron-oxidized bases of thymine, T(N3–H)$^{\bullet}$, and uracil, U(N3–H)$^{\bullet}$, are very close in energy; i.e., the π-radical is only ca. 4 kcal/mol more stable than the σ-radical. For the one-electron-oxidized radicals of cytosine, C$^{\bullet+}$, C(N4–H)$^{\bullet}$, adenine, A$^{\bullet+}$, A(N6–H)$^{\bullet}$, and guanine, G$^{\bullet+}$, G(N2–H)$^{\bullet}$, G(N1–H)$^{\bullet}$, the π-radicals are ca. 16–41 kcal/mol more stable than their corresponding σ-radicals.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Kernel-Based Partial Least Squares: Application to Fingerprint-Based QSAR with Model Visualization

Yuling An, Woody Sherman, and Steven L. Dixon [Schrödinger]

J.Chem. Infor. and Mod. **53**, 2312–2321, 2013.

S!

Numerous regression-based and machine learning techniques are available for the development of linear and nonlinear QSAR models that can accurately predict biological endpoints. Such tools can be quite powerful in the hands of an experienced modeler, but too frequently a disconnect remains between the modeler and project chemist because the resulting QSAR models are effectively black boxes. In this work, we combine direct kernel-based PLS with Canvas 2D fingerprints to arrive at predictive QSAR models that can be projected onto the atoms of a chemical structure, allowing immediate identification of favorable and unfavorable characteristics.

Potentials and Parameters

Dynamic Transition States of ErbB1 Phosphorylation Predicted by Spatial Stochastic Modeling

Meghan McCabe Pryor,Shalini T. Low-Nam,Ádám M. Halász ,Diane S. Lidke, Bridget S. Wilson,Jeremy S. Edwards [University of New Mexico]

Biophysical Journal. **105**, 1533-1543, 2013.

ErbB1 overexpression is strongly linked to carcinogenesis, motivating better understanding of erbB1 dimerization. Recent single-particle-tracking data have provided improved measures of dimer lifetimes and strong evidence that transient receptor coconfinement promotes repeated interactions between erbB1 monomers. Here, spatial stochastic simulations explore the impact of these parameters on erbB1 phosphorylation kinetics. This rule-based model incorporates structural evidence for flux of the erbB1 extracellular domains, as well as asymmetrical orientation of erbB1 cytoplasmic kinase domains during dimerization.

Potentials and Parameters (Cont'd)

Solvent Effects on the Absorption Spectra of the *para*-Coumaric Acid Chromophore in Its Different Protonation Forms

Francisco F. García-Prieto, Ignacio Fdez. Galván, Aurora Muñoz-Losa, Manuel A. Aguilar[Universidad de Extremadura], and M. Elena Martín

J. Chem. Theor. and Comp, **9**, 4481–4494, 2013.

The effects of the solvent and protonation state on the electronic absorption spectrum of the *para*-coumaric acid (pCA), a model of the photoactive yellow protein (PYP), have been studied using the ASEP/MD (averaged solvent electrostatic potential from molecular dynamics) method. Even though, in the protein, the chromophore is assumed to be in its phenolate monoanionic form, when it is found in water solution pH control can favor neutral, monoanionic, and dianionic species. As the pCA has two hydrogens susceptible of deprotonation, both carboxylate and phenolate monoanions are possible. Their relative stabilities are strongly dependent on the medium.

What Is the Dielectric Constant of a Protein When Its Backbone Is Fixed?

Thomas Simonson [DEcole Polytechnique]

J. Chem. Theor. and Comp, **9**, 4603–4608, 2013.

Monte Carlo (MC) simulations with a fixed protein backbone but mobile sidechains are common for acid/base constants and protein design. To characterize the fluctuations in these models, estimating the Fröhlich–Kirkwood dielectric constant can give physical insight and allow comparison both with models that are more rigorous (fully flexible) and ones that are simpler (Poisson–Boltmann without any explicit protein flexibility).

Challenges in Computing Electron-Transfer Energies of DNA Repair Using Hybrid QM/MM Models

Abdul Rehaman Moughal Shahi and Tatiana Domratcheva [Max Planck Institute for Medical Research]

J. Chem. Theor. and Comp, **9**, 4644–4652, 2013.

We studied the effects of ionic groups, that is, a protonated histidine side chain and deprotonated phosphates of DNA, on electron transfer in light-induced DNA repair. On the basis of the X-ray crystal structure, we prepared a hybrid QM/MM model of the macromolecular complex formed between the (6–4) photolyase enzyme and the DNA substrate containing the thymine–thymine (6–4) photoproduct. At the optimized geometries, we computed with the CASSCF and CASPT2 methods the excited states of the electron donor and electron acceptor complex, consisting of the reduced flavin and the (6–4) photoproduct.

Exact Parallel Maximum Clique Algorithm for General and Protein Graphs

Matjaž Depolli, Janez Konc, Kati Rozman, Roman Trobec, and Dušanka Janežič

J.Chem. Infor. and Mod. **53**, 2217–22281, 2013.

A new exact parallel maximum clique algorithm MaxCliquePara, which finds the maximum clique (the fully connected subgraph) in undirected general and protein graphs, is presented. First, a new branch and bound algorithm for finding a maximum clique on a single computer core, which builds on ideas presented in two published state of the art sequential algorithms is implemented. The new sequential MaxCliqueSeq algorithm is faster than the reference algorithms on both DIMACS benchmark graphs as well as on protein-derived product graphs used for protein structural comparisons.

Potentials and Parameters (Cont'd)

Insight into Crizotinib Resistance Mechanisms Caused by Three Mutations in ALK Tyrosine Kinase using Free Energy Calculation Approaches

Huiyong Sun, Youyong Li, Dan Li, and Tingjun Hou [Soochow University]

J.Chem. Infor. and Mod. **53**, 2376–2389, 2013.

As a safe and efficacious drug, crizotinib was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of advanced fusion-type nonsmall-cell lung cancer. Although high response ratio was detected from the patients treated with crizotinib, the cancer has eventually conferred resistance to crizotinib. Several drug resistance mutations have been found in the anaplastic lymphoma kinase (ALK) tyrosine kinase domain as the target for crizotinib, but the drug resistance mechanisms remain unclear. Therefore, in this study, the adaptive biasing force (ABF) method and two-end-state free energy calculation approaches were employed to elucidate the resistance mechanisms of crizotinib induced by the mutations L1152R, G1202R, and S1206Y.

Molecular Dynamics

Molecular Recognition of CXCR4 by a Dual Tropic HIV-1 gp120 V3 Loop

Phanourios Tamamis, Christodoulos A. Floudas [Princeton University]

Biophysical Journal. **105**, 1502-1514, 2013.

HIV-1 cell entry is initiated by the interaction of the viral envelope glycoprotein gp120 with CD4, and chemokine coreceptors CXCR4 and CCR5. We employed a comprehensive set of computational tools, predominantly based on free energy calculations and molecular-dynamics simulations, to investigate the molecular recognition of CXCR4 by a dual tropic V3 loop. We report what is, to our knowledge, the first HIV-1 gp120 V3 loop:CXCR4 complex structure. The computationally derived structure reveals an abundance of polar and nonpolar intermolecular interactions contributing to the HIV-1 gp120:CXCR4 binding. Our results are in remarkable agreement with previous experimental findings.

Mechanisms of Beat-to-Beat Regulation of Cardiac Pacemaker Cell Function by Ca^{2+} Cycling Dynamics

Yael Yaniv, Michael D. Stern, Edward G. Lakatta, Victor A. Maltsev[National Institutes of Health, Baltimore]

Biophysical Journal. **105**, 1551-1561, 2013.

We show that under physiological conditions, application of low concentrations of caffeine (2–4 mM) to isolated single rabbit sinoatrial node cells acutely reduces their spontaneous action potential cycle length (CL) and increases Ca^{2+} transient amplitude for several cycles. Numerical simulations, using a modified Maltsev-Lakatta coupled-clock model, faithfully reproduced these effects, and also the effects of CL prolongation and dysrhythmic spontaneous beating (produced by cytosolic Ca^{2+} buffering) and an acute CL reduction (produced by flash-induced Ca^{2+} release from a caged Ca^{2+} buffer), which we had reported previously.

Molecular Dynamics (Cont'd)

K^+ and Na^+ Conduction in Selective and Nonselective Ion Channels Via Molecular Dynamics Simulations

Simone Furini, Carmen Domene [University of Oxford]

Biophysical Journal. **105**, 1737-1745, 2013.

Generations of scientists have been captivated by ion channels and how they control the workings of the cell by admitting ions from one side of the cell membrane to the other. Elucidating the molecular determinants of ion conduction and selectivity are two of the most fundamental issues in the field of biophysics. In this report, we give an overview of the recent progress made by simulation studies on the understanding of ion permeation in selective and nonselective ion channels.

Molecular Dynamics Simulations of Scorpion Toxin Recognition by the Ca^{2+}-Activated Potassium Channel $K_{Ca}3.1$

Rong Chen [Australian National University], Shin-Ho Chung

Biophysical Journal. **105**, 1829-1837, 2013.

The Ca^{2+}-activated channel of intermediate-conductance ($K_{Ca}3.1$) is a target for antisickling and immunosuppressant agents. Many small peptides isolated from animal venoms inhibit $K_{Ca}3.1$ with nanomolar affinities and are promising drug scaffolds. Although the inhibitory effect of peptide toxins on $K_{Ca}3.1$ has been examined extensively, the structural basis of toxin-channel recognition has not been understood in detail. Here, the binding modes of two selected scorpion toxins, charybdotoxin (ChTx) and OSK1, to human $K_{Ca}3.1$ are examined in atomic detail using molecular dynamics (MD) simulations.

Grcarma: A fully automated task-oriented interface for the analysis of molecular dynamics trajectories

Panagiotis I. Koukos, Nicholas M. Glykos[Democritus University of Thrace]

J. Comp. Chem., **34**, 2310–2312, 2013.

We report the availability of grcarma, a program encoding for a fully automated set of tasks aiming to simplify the analysis of molecular dynamics trajectories of biological macromolecules. It is a cross-platform, Perl/Tk-based front-end to the program carma and is designed to facilitate the needs of the novice as well as those of the expert user, while at the same time maintaining a user-friendly and intuitive design.

Calcium-α-l-Guluronate Complexes: Ca^{2+} Binding Modes from DFT-MD Simulations

Wojciech Plazinski [Polish Academy of Sciences]and Mateusz Drach

J. Phys. Chem. B., **117**, 12105–12112, 2013**.**

The interactions of divalent calcium ions with a single α-L-guluronate anion and oligo(α-L-guluronate) chain have been studied in terms of the 'hybrid' molecular dynamics technique in which the selected parts of the system are treated with different level of theory (DFT-MD). The simulations were focused on obtaining the free energy profiles designed to clarify the possible calcium binding modes. In all considered cases, the calcium ion is coordinated by carboxyl oxygen atoms and water molecules exclusively.

Free Energy Perturbation

Solvation Free Energy of the Peptide Group: Its Model Dependence and Implications for the Additive-Transfer Free-Energy Model of Protein Stability

Dheeraj S. Tomar, D. Asthagiri [Johns Hopkins University], Valéry Weber

Biophysical Journal. **105**, 1482-1490, 2013.

The group-additive decomposition of the unfolding free energy of a protein in an osmolyte solution relative to that in water poses a fundamental paradox: whereas the decomposition describes the experimental results rather well, theory suggests that a group-additive decomposition of free energies is, in general, not valid. In a step toward resolving this paradox, here we study the peptide-group transfer free energy. We calculate the vacuum-to-solvent (solvation) free energies of (Gly)n and cyclic diglycine (cGG) and analyze the data according to experimental protocol.

Overcoming dissipation in the calculation of standard binding free energies by ligand extraction

Camilo Velez-Vega, Michael K. Gilson [University of California San Diego]

J. Comp. Chem., **34**, 2360–2371, 2013.

This article addresses calculations of the standard free energy of binding from molecular simulations in which a bound ligand is extracted from its binding site by steered molecular dynamics (MD) simulations or equilibrium umbrella sampling (US). Host–guest systems are used as test beds to examine the requirements for obtaining the reversible work of ligand extraction. We find that, for both steered MD and US, marked irreversibilities can occur when the guest molecule crosses an energy barrier and suddenly jumps to a new position, causing dissipation of energy stored in the stretched molecule(s)

QM and QM/MM

Long-range corrected density functionals combined with local response dispersion: A promising method for weak interactions

Rahul Kar, Jong-Won Song, Takeshi Sato, Kimihiko Hirao[RIKEN Advanced Institute for Computational Science]

J. Comp. Chem., **34**, 2353–2359, 2013.

Density functional theory, in general, is considered to underestimate the weak van der Waals type of intermolecular interactions. We optimized parameters of the local response dispersion (LRD) method applied to the long-range corrected exchange-correlation functionals (LC-BOP12+LRD and LCgau-BOP+LRD) on the interaction energy for the complexes in the recently compiled S66 database and found to be comparable with the high-level wave function-based methods reported in Řezáč et al. (J. Chem. Theory Comput. **2011**, 7, 2427).

Contributions of pauli repulsions to the energetics and physical properties computed in QM/MM methods

Yingdi Jin, Erin R. Johnson, Xiangqian Hu, Weitao Yang, Hao Hu [The University of Hong Kong]

J. Comp. Chem., **34**, 2380–2388, 2013.

We show here that the LJ potential cannot correctly describe subtle details of the electron density of the QM subsystem because of the neglect of Pauli repulsions between the QM and MM subsystems. The inaccurate electron density subsequently affects the calculation of electronic and magnetic properties of the QM subsystem. To explicitly consider Pauli interactions with QM/MM methods, we propose a method to use empirical effective potentials on the MM atoms.

QM and QM/MM (Cont'd)

Convergence in the QM-only and QM/MM modeling of enzymatic reactions: A case study for acetylene hydratase

Rong-Zhen Liao, Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Comp. Chem., **34**, 2389–2397, 2013.

We report systematic quantum mechanics-only (QM-only) and QM/molecular mechanics (MM) calculations on an enzyme-catalyzed reaction to assess the convergence behavior of QM-only and QM/MM energies with respect to the size of the chosen QM region. The QM and MM parts are described by density functional theory (typically B3LYP/def2-SVP) and the CHARMM force field, respectively. Extending our previous work on acetylene hydratase with QM regions up to 157 atoms (Liao and Thiel, J. Chem. Theory Comput. 2012, 8, 3793), we performed QM/MM geometry optimizations with a QM region **M4** composed of 408 atoms, as well as further QM/MM single-point calculations with even larger QM regions up to 657 atoms.

Quantum Mechanical Study of Vicinal J Spin–Spin Coupling Constants for the Protein Backbone

Bing Wang, Xiao He[East China Normal University], and Kenneth M. Merz

J. Chem. Theor. and Comp, **9**, 4653-4659, 2013.

We have performed densisty functional theory (DFT) calculations of vicinal J coupling constants involving the backbone torsional angle for the protein GB3 using our recently developed automatic fragmentation quantum mechanics/molecular mechanics (AF-QM/MM) approach (Xiao He et al. *J. Phys. Chem. B* **2009**, *113*, 10380–10388). Interestingly, the calculated values based on an NMR structure are more accurate than those based on a high-resolution X-ray structure.

Modeling of Fluorescence Quenching by Lutein in the Plant Light-Harvesting Complex LHCII

C. D. P. Duffy [University of London], J. Chmeliov, M. Macernis, J. Sulskus, L. Valkunas, and A. V. Ruban

J. Phys. Chem. B., **117**, 10974–10986, 2013**.**

Photoprotective non-photochemical quenching (NPQ) in higher plants is the result of the formation of energy quenching traps in the light-harvesting antenna of photosystem II (PSII). It has been proposed that this quenching trap is a lutein molecule closely associated with the chlorophyll terminal emitter of the major light-harvesting complex LHCII. We have used a combination of time-dependent density functional theory (TD-DFT) and the semiempirical MNDO-CAS-CI method to model the chlorophyll–lutein energy transfer dynamics of the highly quenched crystal structure of LHCII.

New Delhi Metallo-β-Lactamase I: Substrate Binding and Catalytic Mechanism

Min Zheng and Dingguo Xu [Sichuan University]

J. Phys. Chem. B., **117**, 11596–11607, 2013**.**

Metallo-β-lactamases can hydrolyze and deactivate lactam-containing antibiotics, which is the major mechanism for causing drug resistance in the treatment of bacterial infections. This has become a global concern because of the lack of clinically approved inhibitors so far. The emergence of New Delhi metallo-β-lactamase I (NDM-1) makes the situation even more serious. In this work, first, the structure of NDM-1 in complex with the inhibitor molecule L-captopril is investigated by both density functional theory (DFT) and hybrid quantum mechanical/molecular mechanical (QM/MM) methods, and the theoretical results are in good agreement with the X-ray structure.

QM and QM/MM (Cont'd)

Simulation of the Amide I Infrared Spectrum in Photoinduced Peptide Folding/Unfolding Transitions

Laura Zanetti-Polzi, Massimiliano Aschi, Andrea Amadei, and Isabella Daidone [University of L'Aquila]

J. Phys. Chem. B., **117**, 12383–12390, 2013**.**

The amide I′ infrared spectrum of a α-helical photoswitchable peptide is calculated here by means of a mixed quantum mechanics/molecular dynamics theoretical–computational methodology based on the perturbed matrix method (PMM). The contribution of specific residues to the total spectrum is also analyzed and the results compared to previous experimental spectroscopic data, obtained by means of site-specific isotope labeling at different residues, resulting in good agreement.

Comparative or Homology Modeling

Computational modeling of human coreceptor CCR5 antagonist as a HIV-1 entry inhibitor: using an integrated homology modeling, docking, and membrane molecular dynamics simulation analysis approach

Changdev G. Gadhe, Gugan Kothandan & Seung Joo Cho [Chosun University]

*J. Biomol. Stru. and Dyn., **31**(11),* 1251-1276, *2013.*

Chemokine receptor 5 (CCR5) is an integral membrane protein that is utilized during human immunodeficiency virus type-1 entry into host cells. CCR5 is a G-protein coupled receptor that contains seven transmembrane (TM) helices. However, the crystal structure of CCR5 has not been reported. A homology model of CCR5 was developed based on the recently reported CXCR4 structure as template. Automated docking of the most potent (**14**), medium potent (**37**), and least potent (**25**) CCR5 antagonists was performed using the CCR5 model. To characterize the mechanism responsible for the interactions between ligands (**14**, **25**, and **37**) and CCR5, membrane MD simulations were performed.

Binding and discerning interactions of PTP1B allosteric inhibitors: Novel insights from molecular dynamics simulations

Ranajit Nivrutti Shinde, M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Graph. and Mod., **45,** 98–110, 2013.

The α7 helix is either disordered or missing in the three co-crystal structures of allosteric inhibitors with protein tyrosine phosphatase 1B (PTP1B). It was modeled in each complex using the open form of PTP1B structure and studied using molecular dynamics (MD) simulations for 25 ns. *B*-factor analysis of the residues sheds light on its disordered nature in the co-crystal structures. Further, the ability of inhibitors to act as allosteric inhibitor was studied and established using novel hydrogen bond criteria.

Structure-based approach to the design of BakBH3 mimetic peptides with increased helical propensity

Laura Delgado-Soler, Maria del Mar Orzaez, Jaime Rubio-Martinez [Universitat de Barcelona]

J. Mol.Mod., **19,** 4305-4318, 2013.

The Bcl-2 family of proteins are well-characterized regulators of the intrinsic apoptotic pathway. Proteins within this family can be classified as either prosurvival or prodeath members and the balance between them present at the mitochondrial membrane is what determines if the cell lives or dies. The use of DFT and *ab initio* computational methods allowed us to perform a thorough conformational study of N-[dihydroxy (methyl)silyl]methylformamide (DHSF) and 3-[dihydroxy (methyl) silyl] propanamide (DHSP), that could be considered simplified models of the environment of the silanediol group in silicon gem-diols that have proven efficiency as protease inhibitors.

Ligand Docking

High-accuracy prediction of transmembrane inter-helix contacts and application to GPCR 3D structure modeling

Jing Yang, Richard Jang, Yang Zhang [University of Michigan], Hong-Bin Shen

Bioinformatics. **29**, 2579-2587, 2013.

Residue–residue contacts across the transmembrane helices dictate the three-dimensional topology of alpha-helical membrane proteins. However, contact determination through experiments is difficult because most transmembrane proteins are hard to crystallize.We present a novel method (MemBrain) to derive transmembrane inter-helix contacts from amino acid sequences by combining correlated mutations and multiple machine learning classifiers. Tested on 60 non-redundant polytopic proteins using a strict leave-one-out cross-validation protocol, MemBrain achieves an average accuracy of 62%, which is 12.5% higher than the current best method from the literature.

Identification of a Common Binding Mode for Imaging Agents to Amyloid Fibrils from Molecular Dynamics Simulations

Katrine Kirkeby Skeby, Jesper Sørensen, and Birgit Schiøtt [Aarhus University]

J. Am. Chem. Soc., 2013, **135**, 15114–15128

S!

Amyloid diseases are characterized by the misfolding and deposition of proteins in the body in the form of insoluble amyloid fibrils. This study uses molecular dynamics simulations to investigate the interactions between 13 aromatic amyloid imaging agents, entailing 4 different organic scaffolds, and a model of an amyloid fibril. Clustering analysis combined with free energy calculations are used to categorize and rank the resulting complexes. Several binding modes are identified across the different ligand scaffolds, however a common favorable binding mode can be identified in which the agent is placed in surface grooves along the amyloid fibril axis.

Modeling iron-catecholates binding to NGAL protein

Cristina Gómez-Casado ,Franziska Roth-Walter ,Erika Jensen-Jarolim, Araceli Díaz-Perales ,Luis F. Pacios [Unidad de Química y Bioquímica]

J. Mol.Graph. and Mod., **45,** 111-121, 2013.

S!

Neutrophil gelatinase associated lipocalin (NGAL) protein is attracting a great interest because of its antibacterial properties played upon modulating iron content in competition against iron acquisition processes developed by pathogenic bacteria that bind selective ferric iron chelators (siderophores). Besides its known high affinity to enterobactin, the most important siderophore, it has been recently shown that NGAL is able to bind Fe(III) coordinated by catechols. The selective binding of Fe(III)-catechol ligands to NGAL is here studied by using iron coordination structures with one, two, and three catecholate ligands.

Searching for Closely Related Ligands with Different Mechanisms of Action Using Machine Learning and Mapping Algorithms

Jenny Balfer, Martin Vogt, and Jürgen Bajorath [Rheinische Friedrich-Wilhelms-Universität,]

J.Chem. Infor. and Mod. **53**, 2252–2274, 2013.

Supervised machine learning approaches, including support vector machines, random forests, Bayesian classifiers, nearest-neighbor similarity searching, and a conceptually distinct mapping algorithm termed DynaMAD, have been investigated for their ability to detect structurally related ligands of a given receptor with different mechanisms of action. For this purpose, a large number of simulated virtual screening trials were carried out with models trained on mechanistic subsets of different classes of receptor ligands.

Ligand Docking (Cont'd)

Computational Profiling of Bioactive Compounds Using a Target-Dependent Composite Workflow

Jamel Meslamani, Ricky Bhajun, Francois Martz, and Didier Rognan [UMR 7200 Université de Strasbourg/CNRS]

J.Chem. Infor. and Mod. **53**, 2322–2333, 2013.

A!

Computational target fishing is a chemoinformatic method aimed at determining main and secondary targets of bioactive compounds in order to explain their mechanism of action, anticipate potential side effects, or repurpose existing drugs for novel therapeutic indications. Many existing successes in this area have been based on a use of a single computational method to estimate potentially new target–ligand associations. We herewith present an automated workflow using several methods to optimally browse target–ligand space according to existing knowledge on either ligand and target space under investigation.

Differential Binding of Latrunculins to G-Actin: A Molecular Dynamics Study

Mohamed A. Helal [Suez Canal University], Sherief Khalifa, and Safwat Ahmed

J.Chem. Infor. and Mod. **53**, 2369-2375, 2013.

S!

Latrunculins are unique macrolides containing a thiazolidinone moiety. Latrunculin A (**1**), latrunculin B (**2**), 16-epi-latrunculin B (**3**), and latrunculin T (**4)** were isolated from the Red Sea sponge *Negombata magnifica*. In the present study, after testing compounds **2**–**4** for cytotoxic activity, they were docked into the crystal structure of G-actin and subjected to binding energy calculation and a 20 ns MD simulation. The modeling study shows that latrunculins binding depends on both hydrophobic interaction of the macrocycle as well as H bonding of the thiazolidinone ring with Asp157 and Thr186.

Ligand Binding Site Detection by Local Structure Alignment and Its Performance Complementarity

Hui Sun Lee [The University of Kansas] and Wonpil Im

J.Chem. Infor. and Mod. **53**, 2462–2470, 2013.

Accurate determination of potential ligand binding sites (BS) is a key step for protein function characterization and structure-based drug design. Despite promising results of template-based BS prediction methods using global structure alignment (GSA), there is room to improve the performance by properly incorporating local structure alignment (LSA) because BS are local structures and often similar for proteins with dissimilar global folds. We present a template-based ligand BS prediction method using G-LoSA, our LSA tool.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 45, October 2013.

84–97 **Design of e-pharmacophore models using compound fragments for the *trans*-sialidase of *Trypanosoma cruzi*: Screening for novel inhibitor scaffolds,** Bill R. Miller III, Adrian E. Roitberg [University of Florida]

See Applications / Medicinal Chemmistry and Drug Design.

98–110 **Binding and discerning interactions of PTP1B allosteric inhibitors: Novel insights from molecular dynamics simulations ,**Ranajit Nivrutti Shinde, M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

See Methodology / Comparative or Homology Modeling

111-121 **Modeling iron-catecholates binding to NGAL protein ,**Cristina Gómez-Casado ,Franziska Roth-Walter ,Erika Jensen-Jarolim, Araceli Díaz-Perales ,Luis F. Pacios [Unidad de Química y Bioquímica]

SeeMethodology / Ligand Docking.

122-127 **The 'order-to-disorder' conformational transition in CD44 protein: An umbrella sampling analysis** ,Wojciech Plazinski [J. Haber Institute of Catalysis and Surface Chemistry] , Agnieszka Knys-Dzieciuch

See Applications / Protein Dynamics.

128–136 **Molecular modeling of enzyme attachment on AFM probes ,**Guedmiller S. Oliveira [Federal University of São Carlos], Fabio L. Leite ,Adriano M. Amarante ,Eduardo F. Franca ,Richard A. Cunha, James M. Briggs ,Luiz C.G. Freitas

See Applications /General and Model Systems.

137–143 **Conformational study of the structure of 18-thiacrown-6 ,**Adel A. El-Azhary [King Saud University]

The study predicted a new C_2conformation as the ground state conformation of 18t6. This new C_2 conformation is more stable than the experimentally known solid state conformation by 4.7 kcal/mol at the MP2/6-311G** level. This conformation has all of the SCCS dihedral angles adopt exodentate structure.

157–172 **3D-QSAR analysis of TRPV1 inhibitors reveals a pharmacophore applicable to diverse scaffolds and clinical candidates ,**Rajendra Kristam ,Vinod Parmar ,Vellarkad N. Viswanadhan[Jubilant Biosys Limited]

See Applications / QSAR.

173–179 **Identification of adenine nucleotide translocase 4 inhibitors by molecular docking ,**Wai-Yee Leung ,Takashi Hamazaki ,David A. Ostrov ,Naohiro Terada [University of Florida College of Medicine]

See Applications / Medicinal Chemmistry and Drug Design.

180–191 **Density functional study of Cu^{2+}-phenylalanine complex under micro-solvation environment** Aravindhan Ganesan [Swinburne University of Technology],Jens Dreyer ,Feng Wang ,Jaakko Akola ,Julen Larrucea

We present an atomistic study carried out using density functional calculations including structural relaxations and Car–Parrinello Molecular Dynamics (CPMD) simulations, aiming to investigate the structures of phenylalanine-copper (II) ($[Phe\text{-}Cu]^{2+}$) complexes and their micro-solvation processes.

192–201 **Exploring the effect of PARP-1 flexibility in docking studies ,**Albert A. Antolin , Andrea Carotti , Roberto Nuti , Aydie Hakkaya ,Emidio Camaioni ,Jordi Mestres ,Roberto Pellicciari ,Antonio Macchiarulo [IMIM Hospital del Mar Research Institute and Universitat Pompeu Fabra]

See Applications / Enzyme Catalysis.

202–210 **Bioisosteric approach in designing new monastrol derivatives: An investigation on their ADMET prediction using in silico derived parameters ,**Syed Fahad Hassan ,Umer Rashid [The University of Lahore,],Farzana Latif Ansari ,Zaheer Ul-Haq

See Applications / Medicinal Chemmistry and Drug Design.

Journal of Computational Chemistry, 34 (26), October 2013.

2223–2232 **1,3-Dipolar cycloadditions of Stone–Wales defective single-walled carbon nanotubes: A theoretical study ,**Tao Yang ,Xiang Zhao [Xi'an Jiaotong University] , Shigeru Nagase

See Applications / Carbon Nanotubes.

2233–2241 **A protocol to evaluate one electron redox potential for iron complexes ,**Hyungjun Kim, Joungwon Park, Yoon Sup Lee[Department of Chemistry, KAIST]

Density functional theory calculation has been performed to calculate the redox potential and the correct ground spin state of iron complexes in acetonitrile. Widely used B3LYP functional is applied with the spin state corrected basis sets.

2242–2248 **Bonding analysis of planar hypercoordinate atoms via the generalized BLW-LOL ,**Laetitia Bomble, Stephan N. Steinmann,Nancy Perez-Peralta, Gabriel Merino ,Clemence Corminboeuf [Institut des Sciences et Ingénierie Chimiques]

The multicenter bonding pattern of the intriguing hexa-, hepta-, and octacoordinate boron wheel series (e.g., CB_6^{2-}, CB_7^-, B_8^{2-}, and SiB_8 as well as the experimentally detected CB_7^- isomer) is revised using the block-localized wave function analyzed by the localized orbital locator (BLW-LOL).

2249–2260 **GPU-accelerated molecular mechanics computations ,**Athanasios Anthopoulos[Cardiff University] ,Ian Grimstead, Andrea Brancale

In this article, we describe an improved cell-list approach designed to match the Kepler architecture of General-purpose graphics processing units (GPGPU). We explain how our approach improves load balancing for the above algorithm and how warp intrinsics are used to implement Newton's third law for the nonbonded force calculations.

2261–2269 **Bond detectors for molecular dynamics simulations, Part I: Hydrogen bonds ,**Anna Stachowicz [Jagiellonian University], Jacek Korchowiec

Charge sensitivity analysis in AMBER force-field resolution has been used in quest for detectors of hydrogen bonds (HBs).

2270–2283 **Ligand release mechanisms and channels in histone deacetylases ,**Subha Kalyaanamoorthy, Yi-Ping Phoebe Chen [La Trobe University]

See Applications / Enzyme Catalysis.

2284–2292 **LIBEFP: A new parallel implementation of the effective fragment potential method as a portable software library ,**Ilya A. Kaliman[Purdue University], Lyudmila V. Slipchenko

See Applications / Bioinformatics.

2293–2309 **New implementation of high-level correlated methods using a general block tensor library for high-performance electronic structure calculations,** Evgeny Epifanovsky, Michael Wormit,Tomasz Kuś, Arie Landau, Dmitry Zuev, Kirill Khistyaev, Prashant Manohar,Ilya Kaliman, Andreas Dreuw, Anna I. Krylov[University of Southern California]

This article presents an open-source object-oriented C++ library of classes and routines to perform tensor algebra.

2310–2312 **Grcarma: A fully automated task-oriented interface for the analysis of molecular dynamics trajectories ,**Panagiotis I. Koukos, Nicholas M. Glykos[Democritus University of Thrace]

See Methodology / Molecular Dynamics.

Journal of Computational Chemistry, 34 (27), October 2013.

2313–2319 **Efficient optimization of van der Waals parameters from bulk properties ,**Steven K. Burger, G. Andrés Cisneros[Wayne State University]

Due to the computational cost involved, when developing a force field for new compounds, one often avoids fitting van der Waals (vdW) terms, instead relying on a general force field based on the atom type. Here, we provide a novel approach to efficiently optimize vdW terms, based on both *ab initio* dimer energies and condensed phase properties.

2389–2397 **Convergence in the QM-only and QM/MM modeling of enzymatic reactions: A case study for acetylene hydratase ,**Rong-Zhen Liao, Walter Thiel [Max-Planck-Institut für Kohlenforschung]

See Methodology / QM and QM/MM.

Journal of Computational Chemistry, 34 (28), October 2013.

2403–2411 **Nuclear quantum effect and temperature dependency on the hydrogen-bonded structure of base pairs ,**Masashi Daido, Yukio Kawashima,Masanori Tachikawa [Yokohama City University]

The structure of Watson–Crick-type adenine-thymine and guanine-cytosine pairs has been studied by hybrid Monte Carlo (HMC) and path integral hybrid Monte Carlo (PIHMC) simulations with the use of semiempirical PM6-DH+ method in the gas phase.

2412–2420 **Efficient lookup table using a linear function of inverse distance squared ,**Jaewoon Jung, Takaharu Mori, Yuji Sugita [RIKEN Theoretical Molecular Science Laboratory]

The major bottleneck in molecular dynamics (MD) simulations of biomolecules exist in the calculation of pairwise nonbonded interactions like Lennard-Jones and long-range electrostatic interactions. Particle-mesh Ewald (PME) method is able to evaluate long-range electrostatic interactions accurately and quickly during MD simulation.

2421–2429 **Bond fukui indices: Comparison of frozen molecular orbital and finite differences through mulliken populations ,**Patrick Bultinck [Ghent University], Sofie Van Damme,Andrés Cedillo

Bond Fukui functions and matrices are introduced for *ab initio* levels of theory using a Mulliken atoms in molecules model. It is shown how these indices may be obtained from first-order density matrix derivatives without need for going to second-order density matrices as in a previous work.

2430–2445 **A computational methodology for accurate predictions of rate constants in solution: Application to the assessment of primary antioxidant activity ,**Annia Galano, Juan Raúl Alvarez-Idaboy [Universidad Nacional Autónoma de México]

The accurate prediction of rate constants for chemical reactions in solution, using computational methods, is a challenging task. In this work, a computational protocol designed to be a reliable tool in the study of radical-molecule reactions in solution is presented.

2446–2459 **Porting ONETEP to graphical processing unit-based coprocessors. 1. FFT box operations ,**Karl Wilkinson, Chris-Kriton Skylaris[University of Southampton]

We present the first graphical processing unit (GPU) coprocessor-enabled version of the Order-N Electronic Total Energy Package (ONETEP) code for linear-scaling first principles quantum mechanical calculations on materials. This work focuses on porting to the GPU the parts of the code that involve atom-localized fast Fourier transform (FFT) operations.

2460–2471 **Electron density deformations provide new insights into the spectral shift of rhodopsins,** Erix Wiliam Hernández-Rodríguez, Ana Lilian Montero-Alejo, Rafael López, Elsa Sánchez-García, Luis Alberto Montero-Cabrera, José Manuel García de la Vega [Universidad Autónoma de Madrid]

Spectral shifts of rhodopsin, which are related to variations of the electron distribution in 11-*cis*-retinal, are investigated here using the method of deformed atoms in molecules. We found that systems carrying the M207R and S186W mutations display large perturbations of the π-conjugated system with respect to wild-type rhodopsin.

2472–2484 **Computational protein design: The proteus software and selected applications ,**Thomas Simonson Ecole Polytechnique, Palaiseau], Thomas Gaillard,David Mignon, Marcel Schmidt am Busch, Anne Lopes, Najette Amara,Savvas Polydorides, Audrey Sedano,Karen Druar, Georgios Archontis

See Applications / Bioinformatics.

2485–2492 Batch tautomer generation with MolTPC ,Thorsten Will, Michael C. Hutter, Johann Jauch, Volkhard Helms [Saarland University]

Besides all their conformational degrees of freedom, drug-like molecules and natural products often also undergo tautomeric interconversions. Compared to the huge efforts made in experimental investigation of tautomerism, open and free algorithmic solutions for prototropic tautomer generation are surprisingly rare.

Journal of Molecular Modeling, 19 (10), October 2013.

4073-4077 **Entropy versus aromaticity in the conformational dynamics of aromatic rings ,**Oleg V. Shishkin [V. N. Karazin Kharkiv National University], Przemyslaw Dopieralski, Irina V. Omelchenko, Leonid Gorb, Zdzislaw Latajka,Jerzy Leszczynski

Comparison of the results of Car-Parrinello molecular dynamics simulations of isolated benzene, pyrimidine and 1,2,4-triazine molecules reveals that the unusually low population of planar geometry of the benzene ring is caused by entropy effects despite its high aromaticity.

4079-4087 **Open carbon frameworks - a search for optimal geometry for hydrogen storage ,**Bogdan Kuchta, Lucyna Firlej, Ali Mohammadhosseini, Matthew Beckner, Jimmy Romanos, Peter Pfeifer

Properties of a new class of hypothetical high-surface-area porous carbons (open carbon frameworks) have been discussed. The limits of hydrogen adsorption in these carbon porous structures have been analyzed in terms of competition between increasing surface accessible for adsorption and the lowering energy of adsorption.

4271-4282 **Molecular dynamics study of Na^+transportation in a cyclic peptide nanotube and its influences on water behaviors in the tube** Xuezeng Song,Jianfen Fan [Soochow University], Dongyan Liu, Hui Li, Rui Li

See Applications / Protein Dynamics.

4283-4291 **Theoretical design of donor-acceptor conjugated copolymers based on furo-, thieno-, and selenopheno[3,4-c] thiophene-4,6-dione and benzodithiophene units for organic solar cells ,**Xiaorui Liu, Rongxing He, Wei Shen, Ming Li [Southwest University]

In this work, a series of donor-acceptor (D-A) copolymers (PBDTFPD(Pa1), PBDTTPD (Pa2) and PBDTSePD(Pa3)) were selected and theoretically investigated using O3LYP/6-31G(d), PBE0/6-31G(d), TD-O3LYP/6-31G(d)//O3LYP/6-31G(d) and periodic boundary conditions methods.

4293-4304 **Stabilizing factors of the molecular structure in silicon-based peptidomimetics in gas-phase and water solution. Assessment of the correlation between different descriptors of hydrogen bond strength** María Pilar Gema Rodríguez Ortega, Manuel Montejo, Juan Jesús López González [University of Jaén]

The use of DFT (B3LYP and M06L) and *ab initio* (MP2) computational methods allowed us to perform a thorough conformational study of N-[dihydroxy (methyl)silyl]methylformamide (DHSF) and 3-[dihydroxy (methyl) silyl] propanamide (DHSP), that could be considered simplified models of the environment of the silanediol group in silicon gem-diols that have proven efficiency as protease inhibitors.

4305-4318 **Structure-based approach to the design of BakBH3 mimetic peptides with increased helical propensity** ,Laura Delgado-Soler, Maria del Mar Orzaez, Jaime Rubio-Martinez [Universitat de Barcelona]

See Methodology / Comparative Or Homology Modelling.

4319-4335 **Self-assembly of cationic surfactants on the carbon nanotube surface: insights from molecular dynamics simulations ,**Niaz Poorgholami-Bejarpasi, Beheshteh Sohrabi [Iran University of Science and Technology]

The insolubility of carbon nanotubes (CNTs) in aqueous media has been a limitation for the practical application of this unique material. To deepen the understanding of molecular interaction between CNT and surfactants, as well as to investigate the influence of the surfactant tail length on the adsorption process, we report here the first detailed large-scale all-atomistic molecular dynamics simulation study of the adsorption and morphology of aggregates of the cationic surfactants containing trimethylammonium headgroups (C_{12}TAB and C_{16}TAB) on single-walled carbon nanotube (SWNT) surfaces.

4349-4368 **Computational design of a full-length model of HIV-1 integrase: modeling of new inhibitors and comparison of their calculated binding energies with those previously studied ,**Selami Ercan, Necmettin Pirinccioglu [University of Dicle]

See Applications / Enzyme Catalysis.

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1. APPLICATIONS

1.1. *Small Molecules*

Water and Solvation

Multiscale Simulation of Liquid Water Using a Four-to-One Mapping for Coarse-Graining

Anu Nagarajan, Christoph Junghans, and Silvina Matysiak [University of Maryland]

J. Chem. Theor. and Comp, **9**, 5168–5175, 2013.

We present a multiresolution simulation scheme for the solvent environment where four atomistic water molecules are mapped onto one coarse-grained bead. We first study the effect of adding restraining potentials in liquid water using full all-atom simulations. The usage of very soft restraining potentials to bundle four nearest neighbor water molecules does not disrupt the hydrogen bonding patterns in the liquid water. The structural properties of the first solvation shell around hydrophobic, hydrophilic, and ionic solutes are well preserved when soft restraining potentials are added.

Medicinal Chemistry and Drug Design

A possible strategy against head and neck cancer: *in silico* investigation of three-in-one inhibitors

Yung-An Tsou, Kuan-Chung Chen, Su-Sen Chang, Yeong-Ray Wen & Calvin Yu-Chian Chen [Asia University]

*J. Biomol. Stru. and Dyn., **31,*** 1358-1369,*2013.*

Overexpression of epidermal growth factor receptor (EGFR), Her2, and uroporphyrinogen decarboxylase (UROD) occurs in a variety of malignant tumor tissues. UROD has potential to modulate tumor response of radiotherapy for head and neck cancer, and EGFR and Her2 are common drug targets for the treatment of head and neck cancer. This study attempts to find a possible lead compound backbone from TCM Database@Taiwan (http://tcm.cmu.edu.tw/) forEGFR, Her2, and UROD proteins against head and neck cancer using computational techniques.

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Medicinal Chemistry and Drug Design (Cont'd)

Structural and functional conservation profiles of novel cathepsin L-like proteins identified in the *Drosophila melanogaster* genome

Sunil Kumar, Rohit Farmer, Andrew P. Turnbull, Niraj Kanti Tripathy & Babu A Manjasetty
[Institute of Life Sciences, Nalco Square, Bhubaneswar]

J. Biomol. Stru. and Dyn., ***31,*** 1481-4898,*2013.*

In this study, five well-characterized cathepsin L proteins from different arthropods were used as query sequences for the *Drosophila* genome database. The search yielded 10 cathepsin L-like sequences, of which eight putatively represent novel cathepsin L-like proteins. To understand the phylogenetic relationship among these cathepsin L-like proteins, a phylogenetic tree was constructed based on their sequences. In addition, models of the tertiary structures of cathepsin L were constructed using homology modeling methods and subjected to molecular dynamics simulations to obtain reasonable structure to understand its dynamical behavior. Our findings demonstrate that all of the potential *Drosophila* cathepsin L-like proteins contain at least one cathepsin propeptide inhibitor domain.

Multi-conformation dynamic pharmacophore modeling of the peroxisome proliferator-activated receptor γ for the discovery of novel agonists

Young-sik Sohn, Chanin Park, Yuno Lee, Songmi Kim, Sundarapandian Thangapandian, Yongseong Kim, Hyong-Ha Kim, Jung-Keun Suh, Keun Woo Lee [Gyeongsang National University (GNU)]

J. Mol.Graph. and Mod., **46,** 1-9, 2013.

In this study, a newly developed approach, multi-conformation dynamic pharmacophore modeling (MCDPM), was used for screening candidate compounds that can properly bind PPARγ. Highly populated structures obtained from molecular dynamics (MD) simulations were selected by clustering analysis. Based on these structures, pharmacophore models were generated from the ligand-binding pocket and then validated to check the rationality.

Novel G-quadruplex stabilizing agents: in-silico approach and dynamics

Rajiv Kumar Kar, Priyanka Suryadevara, Jagannath Jana, Anirban Bhunia & Subhrangsu Chatterjee [Bose Institute]

J. Biomol. Stru. and Dyn., ***31,*** 1497-1518,*2013.*

The stabilization of overhang G-rich repetitive DNA units at the 3′-end of telomeres, which are well known to form functionally important G-quadruplex structures, is a current goal in designing novel anticancer drugs. In the present study, we have undertaken an in silico approach by molecular docking using a small molecule library to find potential G-quadruplex stabilizing agents.

Memory enhancement by traditional Chinese medicine?

I-Chi Hung, Su-Sen Chang, Pei-Chun Chang, Cheng-Chun Lee & Calvin Yu-Chian Chen
[China Medical University Hospital]

J. Biomol. Stru. and Dyn., ***31,*** 1411-1439,*2013.*

Cognitive repair by insulin-like growth factor-I (IGF-I) through activation of insulin-like growth factor-I receptor (IGF-IR) is well established, but not used for clinical therapy due to its link to cancer. We hypothesize that IGF-IR activation rather than IGF-I *per se* may be essential for cognitive repair and attempted to identify ligands from traditional Chinese medicine (TCM) with drug-like potential towards IGF-IR. TCM ligands, 3-(2-carboxyphenyl)-4(3H)-quinazolinone from*Isatisin digotica*, (+)-N-methyllaurotetanine from *Lindera aggregate*, and (+)-1(R)-Coclaurine from*Nelumbonucifera Gaertn*, exhibited high binding affinities and good blood brain barrier (BBB) penetration crucial for accessing IGF-IR.

Medicinal Chemistry and Drug Design (Cont'd)

Binding selectivity studies of PKBα using molecular dynamics simulation and free energy calculations

Shi-Feng Chen, Yang Cao, Jiong-Jiong Chen, Jian-Zhong Chen [Zhejiang University]

J. Mol.Mod., **19,** 5097-5112, 2013.

Designing selective protein kinase B (PKB/Akt) inhibitor is an area of intense research to develop potential anticancer drugs. In the present study, the molecular basis governing PKB-selective inhibition has been investigated using molecular dynamics simulation. The binding free energies calculated by MM/PBSA gave a good correlation with the experimental biological activity and a good explanation of the activity difference of the studied inhibitors.

Noncontiguous Atom Matching Structural Similarity Function

Ana L. Teixeira [University of Lisbon]and Andre O. Falcao

J.Chem. Infor. and Mod. **53**, 2511–2524, 2013.

Measuring similarity between molecules is a fundamental problem in cheminformatics. Given that similar molecules tend to have similar physical, chemical, and biological properties, the notion of molecular similarity plays an important role in the exploration of molecular data sets, query-retrieval in molecular databases, and in structure–property/activity modeling. Various methods to define structural similarity between molecules are available in the literature, but so far none has been used with consistent and reliable results for all situations. We propose a new similarity method based on atom alignment for the analysis of structural similarity between molecules.

Conditional Probabilistic Analysis for Prediction of the Activity Landscape and Relative Compound Activities

Radleigh G. Santos[Torrey Pines Institute for Molecular Studies], Marc A. Giulianotti, Richard A. Houghten, and José L. Medina-Franco

J.Chem. Infor. and Mod. **53**, 2613–2625, 2013.

In this study, we present a novel method of evaluating the ability of a compound comparison methodology to provide accurate information about a set of unknown compounds and also explore the ability of these predicted activity landscapes to prioritize active compounds over inactive. These methods are applied to three distinct and diverse sets of compounds, each with activity data for multiple targets, for a total of eight target-compound set pairs. Six methodologically distinct compound comparison methods were evaluated.

Development and Evaluation of an Integrated Virtual Screening Strategy by Combining Molecular Docking and Pharmacophore Searching Based on Multiple Protein Structures

Sheng Tian, Huiyong Sun, Youyong Li, Peichen Pan, Dan Li, and Tingjun Hou [Zhejiang University]

J.Chem. Infor. and Mod. **53**, 2743–2756, 2013.

In this study, we developed and evaluated a novel parallel virtual screening strategy by integrating molecular docking and complex-based pharmacophore searching based on multiple protein structures. First, the capacity of molecular docking or pharmacophore searching based on any single structure from nine crystallographic structures of Rho kinase 1 (ROCK1) to distinguish the known ROCK1 inhibitors from noninhibitors was evaluated systematically.

S!

Medicinal Chemistry and Drug Design (Cont'd)

Benzazepinones and Benzoxazepinones as Antagonists of Inhibitor of Apoptosis Proteins (IAPs) Selective for the Second Baculovirus IAP Repeat (BIR2) Domain

Andrew F. Donnell [Hoffmann-La Roche Inc], Christophe Michoud, Kenneth C. Rupert, Xiaochun Han, Douglas Aguilar, Karl B. Frank, Adrian J. Fretland, Lin Gao, Barry Goggin, J. Heather Hogg, Kyoungja Hong, Cheryl A. Janson, Robert F. Kester, Norman Kong, Kang Le, Shirley Li, Weiling Liang, Louis J. Lombardo, Yan Lou, Christine M. Lukacs, Steven Mischke, John A. Moliterni, Ann Polonskaia, Andrew D. Schutt, Dave S. Solis, Anthony Specian, Robert T. Taylor, Martin Weisel, and Stacy W. Remiszewski

J.Med.Chem, **56,** 7772–7787, 2013.

This paper details our synthetic explorations of a novel XIAP BIR2-selective benzazepinone screening hit with a focus on increasing BIR2 potency and overcoming high in vivo clearance. These efforts led to the discovery of benzoxazepinone **40**, a potent BIR2-selective inhibitor with good in vivo pharmacokinetic properties which potentiates apoptotic signaling in a manner mechanistically distinct from that of known pan-IAP inhibitors. This paper details our synthetic explorations of a novel XIAP BIR2-selective benzazepinone screening hit with a focus on increasing BIR2 potency and overcoming high in vivo clearance.

Nonhydrolyzable ATP Analogues as Selective Inhibitors of Human NPP1: A Combined Computational/Experimental Study

Joanna Lecka, Gal Ben-David, Luba Simhaev, Shay Eliahu, Jocelyn Oscar, Jr., Patrick Luyindula, Julie Pelletier, Bilha Fischer, Hanoch Senderowitz, and Jean Sévigny [Université Laval]

J.Med.Chem., **56,** 8308–8320, 2013.

Elevated nucleotide pyrophosphatase/phosphodiesterase-1 (NPP1) activity is implicated in health disorders including pathological calcification. Specific NPP1 inhibitors would therefore be valuable for studying this enzyme and as potential therapeutic agents. Here we present a combined computational/experimental study characterizing 13 nonhydrolyzable ATP analogues as selective human NPP1 inhibitors. All analogues at 100 μM inhibited (66–99%) the hydrolysis of pnp-TMP by both recombinant NPP1 and cell surface NPP1 activity of osteocarcinoma (HTB-85) cells.

Binding Mechanism and Synergetic Effects of Xanthone Derivatives as Noncompetitive α-Glucosidase Inhibitors: A Theoretical and Experimental Study

Yan Liu, Lin Ma, Wen-Hua Chen, Hwangseo Park, Zhuofeng Ke, and Bo Wang [Sun Yat-sen University]

J. Phys. Chem. B., **117**, 13464–13471, 2013**.**

Newly emerged xanthone derivatives have attracted considerable interests as a novel class of potent α-glucosidase inhibitors. To provide insights into the inhibitory and binding mechanisms of xanthone-based inhibitors toward α-glucosidase, we carried out experimental and theoretical studies on two typical xanthone derivatives, i.e., 1,3,7-trihydroxyxanthone and 1,3-dihydroxybenzoxanthone. The results indicate that these two xanthone derivatives belong to noncompetitive inhibitors and induce a loss in the α-helix content of the secondary structure of α-glucosidase.

Poly(4-styrenesulfonate) as an Inhibitor of Aβ40 Amyloid Fibril Formation

Bimlesh Ojha, Haiyang Liu, Samrat Dutta, Praveen P. N. Rao, Ewa P. Wojcikiewicz, and Deguo Du[Florida Atlantic University]

J. Phys. Chem. B., **117**, 13975–13984, 2013**.**

The formation of amyloid, a cross-β-sheet fibrillar aggregate of proteins, is associated with a variety of neurodegenerative diseases. Amyloidogenic proteins such as β-amyloid (Aβ) are known to exist with a large amount of polyelectrolyte macromolecules in vivo. The exact nature of Aβ–polyelectrolyte interactions and their roles in Aβ-aggregation are largely unknown. In this regard, we report the inhibiting effect of an anionic polyelectrolyte poly(4-styrenesulfonate) (PSS) on the aggregation of Aβ40 peptide.

Medicinal Chemistry and Drug Design (Cont'd)

Allosteric Inhibition of the NS2B-NS3 Protease from Dengue Virus

Muslum Yildiz, Sumana Ghosh, Jeffrey A. Bell, Woody Sherman, and Jeanne A. Hardy [University of Massachusetts]

ACS Chem. Biol., **8**, article ASAP, 2013.

S!

Dengue virus protease (NS2B-NS3pro) is essential for dengue virus infection and is thus a target of therapeutic interest. To date, attention has focused on developing active-site inhibitors of NS2B-NS3pro. The flat and charged nature of the NS2B-NS3pro active site may contribute to difficulties in developing inhibitors and suggests that a strategy of identifying allosteric sites may be useful. We report an approach that allowed us to scan the NS2B-NS3pro surface by cysteine mutagenesis and use cysteine reactive probes to identify regions of the protein that are susceptible to allosteric inhibition.

Tackling the conformational sampling of larger flexible compounds and macrocycles in pharmacology and drug discovery

I-Jen Chen, Nicolas Foloppe [Vernalis (R&D) Ltd]

Bioorg. and Med.Chem., **21**, 7898-7920, 2013.

S!

Computational conformational sampling underpins much of molecular modeling and design in pharmaceutical work. The sampling of smaller drug-like compounds has been an active area of research. However, few studies have tested in details the sampling of larger more flexible compounds, which are also relevant to drug discovery, including therapeutic peptides, macrocycles, and inhibitors of protein–protein interactions. Here, we investigate extensively mainstream conformational sampling methods on three carefully curated compound sets, namely the 'Drug-like', larger 'Flexible', and 'Macrocycle' compounds.

Quantitative Structure-Activity Relations

Elaborate Ligand-Based Modeling Coupled with Multiple Linear Regression and k Nearest Neighbor QSAR Analyses Unveiled New Nanomolar mTOR Inhibitors

Mohammad A. Khanfar and Mutasem O. Taha [The University of Jordan]

J.Chem. Infor. and Mod. **53**, 2587–2612, 2013.

A!

The mammalian target of rapamycin (mTOR) has an important role in cell growth, proliferation, and survival. mTOR is frequently hyperactivated in cancer, and therefore, it is a clinically validated target for cancer therapy. In this study, we combined exhaustive pharmacophore modeling and quantitative structure–activity relationship (QSAR) analysis to explore the structural requirements for potent mTOR inhibitors employing 210 known mTOR ligands. Genetic function algorithm (GFA) coupled with k nearest neighbor (kNN) and multiple linear re regression (MLR) analyses were employed to build self-consistent and predictive QSAR models based on optimal combinations of pharmacophores and physicochemical descriptors.

Carbon Nanoparticles

Stepwise design of non-covalent wrapping of large diameter carbon nanotubes by peptides

Xin Chen [Henan University], Xiaohan Yu, Yafang Liu, Jinglai Zhang

J. Mol.Graph. and Mod., **46,** 83-92, 2013.

Single-walled carbon nanotube (SWCNT) is one of the most popular low-dimensional carbon materials in material science, nanomedicine, and nanoscale electronics. Yet the application of the SWCNTs was hindered by the self-aggregation. To purify and disperse the SWCNTs, non-covalent wrapping is one of the effective options to overcome such defects. In this work, two kinds of short peptides were designed to facilitate the modification of large-diameter SWCNT.

1.2. *Biopolymers*

Bioinformatics and Cheminformatics

***cat*RAPID *omics*: a web server for large-scale prediction of protein–RNA interactions**

Federico Agostini, Andreas Zanzoni, Petr Klus, Domenica Marchese, Davide Cirillo, Gian Gaetano Tartaglia [Universitat Pompeu Fabra (UPF)]

Bioinformatics. **29**, 2928-2930, 2013.

We developed a web server to allow fast calculation of ribonucleoprotein associations in *Caenorhabditis elegans*, *Danio rerio*, *Drosophila melanogaster*, *Homo sapiens*, *Mus musculus*, *Rattus norvegicus*, *Saccharomyces cerevisiae* and *Xenopus tropicalis* (custom libraries can be also generated). The *cat*RAPID *omics* was benchmarked on the recently published RNA interactomes of Serine/arginine-rich splicing factor 1 (SRSF1), Histone-lysine N-methyltransferase EZH2 (EZH2), TAR DNA-binding protein 43 (TDP43) and RNA-binding protein FUS (FUS) as well as on the protein interactomes of U1/U2 small nucleolar RNAs, X inactive specific transcript (Xist) repeat A region (RepA) and Crumbs homolog 3 (CRB3) 3′-untranslated region RNAs.

TALENoffer: genome-wide TALEN off-target prediction

Jan Grau [Martin Luther University Halle–Wittenberg], Jens Boch, Stefan Posch

Bioinformatics. **29**, 2931-2932, 2013.

Transcription activator-like effector nucleases (TALENs) have become an accepted tool for targeted mutagenesis, but undesired *off-targets* remain an important issue. We present TALENoffer, a novel toolfor the genome-wide prediction of TALEN off-targets. We show that TALENoffer successfully predicts known off-targets of engineered TALENs and yields a competitive runtime, scanning complete mammalian genomes within a few minutes.

Bioinformatics and Cheminformatics (Cont'd)

RNAfbinv: an interactive Java application for fragment-based design of RNA sequences

Lina Weinbrand, Assaf Avihoo, Danny Barash[Ben Gurion University of the Negev]

Bioinformatics. **29**, 2938-2940, 2013.

In RNA design problems, it is plausible to assume that the user would be interested in preserving a particular RNA secondary structure motif, or fragment, for biological reasons. The preservation could be in structure or sequence, or both. We have developed a new interactive Java application called RNA fragment-based inverse that allows users to insert an RNA secondary structure in dot-bracket notation. It then performs sequence design that conforms to the shape of the input secondary structure, the specified thermodynamic stability, the specified mutational robustness and the user-selected fragment after shape decomposition.

DNABind: A hybrid algorithm for structure-based prediction of DNA-binding residues by combining machine learning- and template-based approaches

Rong Liu, Jianjun Hu [University of South Carolina]

Proteins: Stru. Fun. & Bioinf., **81**, 1885–1899, 2013.

Accurate prediction of DNA-binding residues has become a problem of increasing importance in structural bioinformatics. Here, we presented DNABind, a novel hybrid algorithm for identifying these crucial residues by exploiting the complementarity between machine learning- and template-based methods. Our machine learning-based method was based on the probabilistic combination of a structure-based and a sequence-based predictor, both of which were implemented using support vector machines algorithms.

Estimating Error Rates in Bioactivity Databases

Pekka Tiikkainen [Merz Pharmaceuticals GmbH], Louisa Bellis, Yvonne Light, and Lutz Franke

J.Chem. Infor. and Mod. **53**, 2499–2505, 2013.

Bioactivity databases are routinely used in drug discovery to look-up and, using prediction tools, to predict potential targets for small molecules. These databases are typically manually curated from patents and scientific articles. Apart from errors in the source document, the human factor can cause errors during the extraction process. These errors can lead to wrong decisions in the early drug discovery process. In the current work, we have compared bioactivity data from three large databases (ChEMBL, Liceptor, and WOMBAT) who have curated data from the same source documents.

Automated Extraction of Information on Chemical–P-glycoprotein Interactions from the Literature

Shuya Yoshida, Fumiyoshi Yamashita [Kyoto University], Atsushi Ose, Kazuya Maeda, Yuichi Sugiyama, and Mitsuru Hashida

J.Chem. Infor. and Mod. **53**, 22506–2510 , 2013.

Knowledge of the interactions between drugs and transporters is important for drug discovery and development as well as for the evaluation of their clinical safety. We recently developed a text-mining system for the automatic extraction of information on chemical–CYP3A4 interactions from the literature. This system is based on natural language processing and can extract chemical names and their interaction patterns according to sentence context. The present study aimed to extend this system to the extraction of information regarding chemical–transporter interactions.

Bioinformatics and Cheminformatics (Cont'd)

Identification of New Fyn Kinase Inhibitors Using a FLAP-Based Approach

Giulio Poli, Tiziano Tuccinardi [University of Pisa], Flavio Rizzolio, Isabella Caligiuri, Lorenzo Botta, Carlotta Granchi, Gabriella Ortore, Filippo Minutolo, Silvia Schenone, and Adriano Martinelli

J.Chem. Infor. and Mod. **53**, 2538-2547, 2013.

The abnormal activity of Fyn tyrosine kinase has been shown to be related to various human cancers. Furthermore, its involvement in signaling pathways that lead to severe pathologies, such as Alzheimer's and Parkinson's diseases, has also been demonstrated, thus making Fyn an attractive target for the discovery of potential novel therapeutics for brain pathologies and tumors. In this study we evaluated the reliability of various screening approaches based on the FLAP software.

Searching for Likeness in a Database of Macromolecular Complexes

Jeffrey R. Van Voorst and Barry C. Finzel [University of Minnesota College of Pharmacy]

J.Chem. Infor. and Mod. **53**, 2634–2647, 2013.

A software tool and workflow based on distance geometry is presented that can be used to search for local similarity in substructures in a comprehensive database of experimentally derived macromolecular structure. The method does not rely on fold annotation, specific secondary structure assignments, or sequence homology and may be used to locate compound substructures of multiple segments spanning different macromolecules that share a queried backbone geometry.

Molecular Dynamics-Based Virtual Screening: Accelerating the Drug Discovery Process by High-Performance Computing

Hu Ge, Yu Wang, Chanjuan Li, Nanhao Chen, Yufang Xie, Mengyan Xu, Yingyan He, Xinchun Gu, Ruibo Wu, Qiong Gu, Liang Zeng, and Jun Xu [Sun Yat-Sen University]

J.Chem. Infor. and Mod. **53**, 2757–2764, 2013.

High-performance computing (HPC) has become a state strategic technology in a number of countries. One hypothesis is that HPC can accelerate biopharmaceutical innovation. Our experimental data demonstrate that HPC can significantly accelerate biopharmaceutical innovation by employing molecular dynamics-based virtual screening (MDVS). Without using HPC, MDVS for a 10K compound library with tens of nanoseconds of MD simulations requires years of computer time. . In contrast, a state of the art HPC can be 600 times faster than an eight-core PC server is in screening a typical drug target (which contains about 40K atoms).

Development of an Informatics Platform for Therapeutic Protein and Peptide Analytics

Mark R. Hansen and Hugo O. Villar [Altoris], Eric Feyfant

J.Chem. Infor. and Mod. **53**, 2774–2779, 2013.

The momentum gained by research on biologics has not been met yet with equal thrust on the informatics side. There is a noticeable lack of software for data management that empowers the bench scientists working on the development of biologic therapeutics. SARvision|Biologics is a tool to analyze data associated with biopolymers, including peptides, antibodies, and protein therapeutics programs. The program brings under a single user interface tools to filter, mine, and visualize data as well as those algorithms needed to organize sequences.

Bioinformatics and Cheminformatics (Cont'd)

Accelerated Molecular Dynamics Simulations with the AMOEBA Polarizable Force Field on Graphics Processing Units

Steffen Lindert [University of California San Diego], Denis Bucher, Peter Eastman, Vijay Pande, and J. Andrew McCammon

J. Chem. Theor. and Comp, **9**, 4684–4691, 2013.

The accelerated molecular dynamics (aMD) method has recently been shown to enhance the sampling of biomolecules in molecular dynamics (MD) simulations, often by several orders of magnitude. Here, we describe an implementation of the aMD method for the OpenMM application layer that takes full advantage of graphics processing units (GPUs) computing. The aMD method is shown to work in combination with the AMOEBA polarizable force field (AMOEBA-aMD), allowing the simulation of long time-scale events with a polarizable force field.

Optimization of Umbrella Sampling Replica Exchange Molecular Dynamics by Replica Positioning

Danial Sabri Dashti and Adrian E. Roitberg

J. Chem. Theor. and Comp, **9**, 4692–4699, 2013.

The positioning of sampling windows in an umbrella sampling simulation has an effect on the rate of convergence and computational efficiency. When such simulation is coupled with a Hamiltonian replica exchange setup, we show that such positioning can be optimized for maximal convergence of the results. We present a method for estimating the exchange acceptance ratio (EAR) between two arbitrary positions on a reaction coordinate in umbrella sampling replica exchange (USRE) molecular dynamics (MD). We designed a scoring function to optimize the position of the set of replicas (windows).

Isosteric and Nonisosteric Base Pairs in RNA Motifs: Molecular Dynamics and Bioinformatics Study of the Sarcin–Ricin Internal Loop

Marek Havrila, Kamila Réblová, Craig L. Zirbel, Neocles B. Leontis, and Jiří Šponer [Masaryk University]

J. Phys. Chem. B., **117**, 14302–14319, 2013**.**

The sarcin–ricin RNA motif (SR motif) is one of the most prominent recurrent RNA building blocks that occurs in many different RNA contexts and folds autonomously, that is, in a context-independent manner. In this study, we combined bioinformatics analysis with explicit-solvent molecular dynamics (MD) simulations to better understand the relation between the RNA sequence and the evolutionary patterns of the SR motif. A SHAPE probing experiment was also performed to confirm the fidelity of the MD simulations. We identified 57 instances of the SR motif in a nonredundant subset of the RNA X-ray structure database and analyzed their base pairing, base–phosphate, and backbone–backbone interactions.

Protein Confirmational Analysis

Conformational flexibility of the leucine binding protein examined by protein domain coarse-grained molecular dynamics

Iwona Siuda, Lea Thøgersen [Aarhus University]

J. Mol.Mod., **19,** 4931-4945, 2013.

Periplasmic binding proteins are the initial receptors for the transport of various substrates over the inner membrane of gram-negative bacteria. The binding proteins are composed of two domains, and the substrate is entrapped between these domains. For several of the binding proteins it has been established that a closed-up conformation exists even without substrate present, suggesting a highly flexible apo-structure which would compete with the ligand-bound protein for the transporter interaction. Here we present molecular dynamics simulations exploring the conformational flexibility of LBP

Conformational Dynamics of the Partially Disordered Yeast Transcription Factor GCN4

Paul Robustelli, Nikola Trbovic, Richard A. Friesner, and Arthur G. Palmer, III [Columbia University]

J. Chem. Theor. and Comp, **9**, 5190–5200, 2013.

S!

Molecular dynamics (MD) simulations have been employed to study the conformational dynamics of the partially disordered DNA binding basic leucine zipper domain of the yeast transcription factor GCN4. We demonstrate that back-calculated NMR chemical shifts and spin-relaxation data provide complementary probes of the structure and dynamics of disordered protein states and enable comparisons of the accuracy of multiple MD trajectories.

Population Based Reweighting of Scaled Molecular Dynamics

William Sinko[University of California San Diego], Yinglong Miao, César Augusto F. de Oliveira, and J. Andrew McCammon

J. Phys. Chem. B., **117**, 12759–12768, 2013**.**

Molecular dynamics simulation using enhanced sampling methods is one of the powerful computational tools used to explore protein conformations and free energy landscapes. Enhanced sampling methods often employ either an increase in temperature or a flattening of the potential energy surface to rapidly sample phase space, and a corresponding reweighting algorithm is used to recover the Boltzmann statistics. We propose a scaled molecular dynamics method, which modifies the biomolecular potential energy surface and employs a reweighting scheme based on configurational populations.

The Conformational Landscape of an Intrinsically Disordered DNA-Binding Domain of a Transcription Regulator

Athi N. Naganathan and Modesto Orozco [University of Barcelona]

J. Phys. Chem. B., **117**, 13842–13850, 2013**.**

S!

Delineating the conformational features of intrinsically disordered proteins (IDPs) is an area of work that challenges current experimental and simulation protocols. It is therefore imperative to combine multiple methodologies to arrive at a coherent picture of the heterogeneous IDP ensembles. Here, we present a comprehensive study drawing from structure-based statistical mechanical model, explicit-solvent MD and implicit-solvent REMD simulations, and mutational analysis to characterize, in combination with experimental observables, the functional landscape of the intrinsically disordered DNA-binding domain (DBD) of the *Escherichia coli* transcription regulator CytR in its free-state.

Protein Structure Analysis

Structural insights into the South African HIV-1 subtype C protease: impact of hinge region dynamics and flap flexibility in drug resistance

Previn Naicker, Ikechukwu Achilonu, Sylvia Fanucchi, Manuel Fernandes, Mahmoud A.A. Ibrahim, Heini W. Dirr, Mahmoud E.S. Soliman & Yasien Sayed [University of Witwatersrand]

J. Biomol. Stru. and Dyn., ***31,*** 1370-1380,*2013.*

The HIV protease plays a major role in the life cycle of the virus and has long been a target in antiviral therapy. Resistance of HIV protease to protease inhibitors (PIs) is problematic for the effective treatment of HIV infection. The South African HIV-1 subtype C protease (C-SA PR), which contains eight polymorphisms relative to the consensus HIV-1 subtype B protease, was expressed in *Escherichia coli*, purified, and crystallized. The crystal structure of the C-SA PR was resolved at 2.7 Å, which is the first crystal structure of a HIV-1 subtype C protease that predominates in Africa.

Insight into the structural stability of wild type and mutants of the tobacco etch virus protease with molecular dynamics simulations

Yu Wang, Guo-Fei Zhu, Si-Yan Ren, Yong-Guang Han, Yue Luo, Lin-Fang Du [Sichuan University]

J. Mol.Mod., **19,** 4865-4875, 2013.

A!

The efficiency and high specificity of tobacco etch virus protease (TEVp) has made it widely used for cleavage of recombinant fusion proteins. However, TEVp suffers from a few intrinsic defects such as self-cleavage, poorly expressed in *E. coli* and less soluble. So some mutants were designed to improve it, such as S219V, T17S/N68D/I77V and L56V/S135G etc. MD simulations for the WT TEVp and its mutants were performed to explore the underlying dynamic effects of mutations on TEVp.

Structural Intermediates and Folding Events in the Early Assembly of the Ribosomal Small Subunit

Jonathan Lai, Ke Chen, and Zaida Luthey-Schulten [University of Illinois at Urbana−Champaign]

J. Phys. Chem. B., **117**, 13335–13345, 2013**.**

Using all-atom explicit solvent molecular dynamics (MD) simulations, we investigated the early structural intermediates of the 5′ domain of the 16S rRNA in *Escherichia coli* upon the removal of the primary binding r-proteins S4, S17, and S20 and the secondary binding r-protein S16. Removal of each r-protein corresponded to the disappearance of subdomains with correlated dynamics. Correlation-based network analysis of the MD trajectories of the naked rRNA showed that the different subdomains are connected via multiple pathways with high betweenness.

Protein Dynamics

Activation and Proton Transport Mechanism in Influenza A M2 Channel

Chenyu Wei, Andrew Pohorille [University of California]

Biophysical Journal. **105**, 2036–2045, 2013.

Molecular dynamics trajectories 2 μs in length have been generated for the pH-activated, tetrameric M2proton channel of the influenza A virus in all protonation states of the pH sensor located at the His^{37} tetrad. All simulated structures are in very good agreement with high-resolution structures. Changes in the channel caused by progressive protonation of His^{37} provide insight into the mechanism of proton transport

Protein Dynamics (Cont'd)

Molecular Simulations of a Dynamic Protein Complex: Role of Salt-Bridges and Polar Interactions in Configurational Transitions

Liqun Zhang, Matthias Buck [Case Western Reserve University]

Biophysical Journal. **105**, 2412–2417, 2013.

Ion charge pairs and hydrogen bonds have been extensively studied for their roles in stabilizing protein complexes and in steering the process of protein association. We have previously characterized one such system: the EphA2:SHIP2 SAM-SAM heterodimer by solution NMR. Here we carried out extensive all-atom molecular-dynamics simulations on a microsecond time-scale starting with different NMR-derived structures for the complex. Transitions are observed between several discernible configurations at average time intervals of 50–100 ns. The domains reorient relative to one another by substantial rotation and a slight shifting of the interfaces.

Monte carlo simulations of proteins at constant pH with generalized born solvent, flexible sidechains, and an effective dielectric boundary

Savvas Polydorides, Thomas Simonson [Ecole Polytechnique]

J. Comp. Chem., **34**, 2742–2756 , 2013.

Titratable residues determine the acid/base behavior of proteins, strongly influencing their function; in addition, proton binding is a valuable reporter on electrostatic interactions. We describe a method for pK_a calculations, using constant-pH Monte Carlo (MC) simulations to explore the space of sidechain conformations and protonation states, with an efficient and accurate generalized Born model (GB) for the solvent effects. To overcome the many-body dependency of the GB model, we use a "Native Environment" approximation, whose accuracy is shown to be good.

Interaction of organic solvents with protein structures at protein-solvent interface

Morteza Khabiri, Babak Minofar, Jan Brezovský, Jiří Damborský, Rudiger Ettrich [University of South Bohemia in Ceske Budejovice]

J. Mol.Mod., **19,** 4701-4711, 2013.

The effect of non-denaturing concentrations of three different organic solvents, formamide, acetone and isopropanol, on the structure of haloalkane dehalogenases DhaA, LinB, and DbjA at the protein-solvent interface was studied using molecular dynamics simulations. Analysis of B-factors revealed that the presence of a given organic solvent mainly affects the dynamical behavior of the specificity-determining cap domain, with the exception of DbjA in acetone.

S!

The intrinsic helical propensities of the helical fragments in prion protein under neutral and low pH conditions: a replica exchange molecular dynamics study

Xiaoliang Lu, Juan Zeng, Ya Gao, John Z. H. Zhang, Dawei Zhang, Ye Mei[East China Normal University]

J. Mol.Mod., **19,** 4897-4908, 2013.

Replica exchange molecular dynamics simulations in neutral and acidic aqueous solutions were employed to study the intrinsic helical propensities of three helices in both Syrian hamster (syPrP) and human (huPrP) prion proteins. The helical propensities of syPrP HA and huPrP HA are very high under both pH conditions, which implies that HA is barely involved in the helix-to-β transition.

Protein Dynamics (Cont'd)

Combining Solvent Thermodynamic Profiles with Functionality Maps of the Hsp90 Binding Site to Predict the Displacement of Water Molecules

Kamran Haider and David J. Huggins [Lahore University of Management Sciences]

J.Chem. Infor. and Mod. **53**, 2571–2586, 2013.

Intermolecular interactions in the aqueous phase must compete with the interactions between the two binding partners and their solvating water molecules. In biological systems, water molecules in protein binding sites cluster at well-defined hydration sites and can form strong hydrogen-bonding interactions with backbone and side-chain atoms. Displacement of such water molecules is only favorable when the ligand can form strong compensating hydrogen bonds. In this study, we employed IFST to study the displacement of water molecules from the ATP binding site of Hsp90, using a test set of 103 ligands.

Specialized Dynamical Properties of Promiscuous Residues Revealed by Simulated Conformational Ensembles

Arianna Fornili, Alessandro Pandini, Hui-Chun Lu, and Franca Fraternali [King's College London]

J. Chem. Theor. and Comp, **9**, 5127–5147, 2013.

Here, we present the first comprehensive study of the intrinsic dynamics of promiscuous residues in a large protein data set. Different computational methods, from coarse-grained elastic models to geometry-based sampling methods and to full-atom Molecular Dynamics simulations, were used to generate conformational ensembles for the isolated proteins. The flexibility and dynamic correlations of interface residues with a different degree of binding promiscuity were calculated and compared considering side chain and backbone motions, the latter both on a local and on a global scale.

Predicting the Thermodynamics and Kinetics of Helix Formation in a Cyclic Peptide Model

João M. Damas, Luís C.S. Filipe, Sara R.R. Campos, Diana Lousa, Bruno L. Victor, António M. Baptista, and Cláudio M. Soares [Universidade Nova de Lisboa]

J. Chem. Theor. and Comp, **9**, 5148–5157, 2013.

The peptide Ac-(*cyclo*-2,6)-R[KAAAD]-NH_2 (*cyc*-RKAAAD) is a short cyclic peptide known to adopt a remarkably stable single turn α-helix in water. Due to its simplicity and the availability of thermodynamic and kinetic experimental data, *cyc*-RKAAAD poses as an ideal model for evaluating the aptness of current molecular dynamics (MD) simulation methodologies to accurately sample conformations that reproduce experimentally observed properties. In this work, we extensively sample the conformational space of *cyc*-RKAAAD using microsecond-timescale MD simulations.

Probing the Physical Determinants of Thermal Expansion of Folded Proteins

Mariano Dellarole **,** Kei Kobayashi **,** Jean-Baptiste Rouget **,** José Alfredo Caro **,** Julien Roche **,**Mohammad M. Islam **,** Bertrand Garcia-Moreno E.**,** Yutaka Kuroda **,** Catherine A. Royer **[**Université Montpellier 1 & 2]

J. Phys. Chem. B., **117**, 12742–12749, 2013**.**

The magnitude and sign of the volume change upon protein unfolding are strongly dependent on temperature. This temperature dependence reflects differences in the thermal expansivity of the folded and unfolded states. The factors that determine protein molar expansivities and the large differences in thermal expansivity for proteins of similar molar volume are not well understood. Here, the contribution from hydration density to the molar thermal expansivity of a protein was examined by comparing bovine pancreatic trypsin inhibitor and variants with alanine substitutions at or near the protein–water interface.

Protein Dynamics (Cont'd)

Intramolecular Distances and Dynamics from the Combined Photon Statistics of Single-Molecule FRET and Photoinduced Electron Transfer

Dominik Haenni, Franziska Zosel, Luc Reymond, Daniel Nettels[University of Zurich,], and Benjamin Schuler

J. Phys. Chem. B., **117**, 13015–13028, 2013**.**

Single-molecule Förster resonance energy transfer (FRET) and photoinduced electron transfer (PET) have developed into versatile and complementary methods for probing distances and dynamics in biomolecules. Here we show that the two methods can be combined in one molecule to obtain both accurate distance information and the kinetics of intramolecular contact formation. In a first step, we show that the fluorescent dyes Alexa 488 and Alexa 594, which are frequently used as a donor and acceptor for single-molecule FRET, are also suitable as PET probes with tryptophan as a fluorescence quencher.

Gradual Disordering of the Native State on a Slow Two-State Folding Protein Monitored by Single-Molecule Fluorescence Spectroscopy and NMR

Luis A. Campos, Mourad Sadqi, Jianwei Liu, Xiang Wang, Douglas S. English, and Victor Muñoz[Consejo Superior de Investigaciones Científicas]

J. Phys. Chem. B., **117**, 13120–13131, 2013**.**

Theory predicts that folding free energy landscapes are intrinsically malleable and as such are expected to respond to perturbations in topographically complex ways. Structural changes upon perturbation have been observed experimentally for unfolded ensembles, folding transition states, and fast downhill folding proteins. However, the native state of proteins that fold in a two-state fashion is conventionally assumed to be structurally invariant during unfolding. Here we investigate how the native and unfolded states of the chicken α-spectrin SH3 domain (a well characterized slow two-state folder) change in response to chemical denaturants and/or temperature.

Free Energy Calculations

Absolute free energies of biomolecules from unperturbed ensembles

Gevorg Grigoryan [Dartmouth College]

J. Comp. Chem., **34**, 2726–2741, 2013.

Computing the absolute free energy of a macromolecule's structural state, *F*, is a challenging problem of high relevance. This study presents a method that computes *F* using only information from an unperturbed simulation of the macromolecule in the relevant conformational state, ensemble, and environment. Absolute free energies produced by this method, dubbed Valuation of Local Configuration Integral with Dynamics (VALOCIDY), enable comparison of alternative states.

Could MM-GBSA be accurate enough for calculation of absolute protein/ligand binding free energies?

Chandrika Mulakala [Jubilant Biosys Limited], Vellarkad N. Viswanadhan

J. Mol.Graph. and Mod., **46,** 41-51, 2013.

S!

Implicit solvation methods such as MM-GBSA, when applied to evaluating protein/ligand binding free energies, are widely believed to be accurate only for the estimation of relative binding free energies for a congeneric series of ligands. In this work, we show that the MM-GBSA flavor of Prime 3.0, VSGB-2.0, with a variable dielectric model and a novel energy function, could be approaching the accuracy required for evaluating absolute binding free energies, albeit, through a linear regression fit.

Ligand Binding/Docking

Anomalous versus Slowed-Down Brownian Diffusion in the Ligand-Binding Equilibrium

Hédi Soula, Bertrand Caré, Guillaume Beslon, Hugues Berry [Université de Lyon]

Biophysical Journal. **105**, 2064–2073, 2013.

Measurements of protein motion in living cells and membranes consistently report transient anomalous diffusion (subdiffusion) that converges back to a Brownian motion with reduced diffusion coefficient at long times after the anomalous diffusion regime. We compare the (long-time) equilibrium properties obtained with transient anomalous diffusion due to obstacle hindrance or power-law-distributed residence times (continuous-time random walks) to those obtained with space-dependent slowed-down Brownian motion. Using theoretical arguments and Monte Carlo simulations, we show that these three scenarios have distinctive effects on the apparent affinity of the reaction.

Stereoselectivity of chalcone isomerase with chalcone derivatives: a computational study

Yuan Yao, Hui Zhang, Ze-Sheng Li [Harbin Institute of Technology]

J. Mol.Mod., **19,** 4753-4761, 2013.

Chalcone isomerase (CHI) catalyzes the intramolecular cyclization of chalcones into flavonoids. The activity of CHI is essential for the biosynthesis of flavonoids precursors of floral pigments and phenylpropanoid plant defense compounds. In the present study, we explored the detailed binding structures and binding free energies for two different active site conformations of CHI with *s*-cis/*s*-trans conformers of three chalcone compounds by performing molecular dynamics (MD) simulations and binding free energy calculations.

Ligand binding and dynamics of the monomeric epidermal growth factor receptor ectodomain

Hannes H. Loeffler[STFC Daresbury], Martyn D. Winn

Proteins: Stru. Fun. & Bioinf., **81**, 1931–1943, 2013.

The ectodomain of the human epidermal growth factor receptor (hEGFR) controls input to several cell signalling networks via binding with extracellular growth factors. To gain insight into the dynamics and ligand binding of the ectodomain, the hEGFR monomer was subjected to molecular dynamics simulation. The monomer was found to be substantially more flexible than the ectodomain dimer studied previously.

Binding of modulators to mouse and human multidrug resistance P-glycoprotein. A computational study

Gabriel E. Jara, D. Mariano A. Vera [Universidad Nacional de Mar del Plata], Adriana B. Pierini

J. Mol.Graph. and Mod., **46,** 10-21, 2013.

The human multidrug resistance (MDR) P-glycoprotein (P-gp) mediates the extrusion of chemotherapeutic drugs from cancer cells. Modulators are relevant pharmaceutical targets since they are intended to control or to inhibit its pumping activity. In the present work, a common binding site for Rhodamine 123 and modulators with different modulation activity was found by molecular docking over the crystal structure of the mouse P-gp.

Ligand Binding / Docking (Cont'd)

MMGBSA As a Tool To Understand the Binding Affinities of Filamin–Peptide Interactions

Mikko Ylilauri and Olli T. Pentikäinen [University of Jyväskylä]

J.Chem. Infor. and Mod. **53**, 2626–2633, 2013.

We computationally estimated the binding free energies of filamin A (FLNa) subunits with bound peptides using the molecular mechanics-generalized Born surface area (MMGBSA) method. The obtained computational results correlated well with the experimental data, and they ranked efficiently both the binding of one ligand to all used FLNa-domains and the binding of all used ligands to FLNa21. Furthermore, the steered molecular dynamics (SMD) simulations pinpointed the binding hot spots for these complexes.

Ligand-Induced Structural Changes in TEM-1 Probed by Molecular Dynamics and Relative Binding Free Energy Calculations

A. C. Pimenta, J. M. Martins, R. Fernandes, and I. S. Moreira [Faculdade de Ciências da Universidade do Porto]

J.Chem. Infor. and Mod. **53**, 2648-2658 , 2013.

S!

The TEM family of enzymes has had a crucial impact on the pharmaceutical industry due to their important role in antibiotic resistance. Even with the latest technologies in structural biology and genomics, no 3D structure of a TEM-1/antibiotic complex is known previous to acylation. Therefore, the comprehension of their capability in acylate antibiotics is based on the protein macromolecular structure uncomplexed. In this work, molecular docking, molecular dynamic simulations, and relative free energy calculations were applied in order to get a comprehensive and thorough analysis of TEM-1/ampicillin and TEM-1/amoxicillin complexes.

Computational Study of the $Fe(CN)_2CO$ Cofactor and Its Binding to HypC Protein

Marta Albareda, Jose-Manuel Palacios, Juan Imperial, and Luis F. Pacios [Universidad Politécnica de Madrid (UPM)]

J. Phys. Chem. B., **117**, 13523–13533, 2013**.**

In the intricate maturation process of [NiFe]-hydrogenases, the $Fe(CN)_2CO$ cofactor is first assembled in a HypCD complex with iron coordinated by cysteines from both proteins and CO is added after ligation of cyanides. The small accessory protein HypC is known to play a role in delivering the cofactor needed for assembling the hydrogenase active site. However, the chemical nature of the $Fe(CN)_2CO$ moiety and the stability of the cofactor–HypC complex are open questions. In this work, we address geometries, properties, and the nature of bonding of all chemical species involved in formation and binding of the cofactor by means of quantum calculations.

Enzyme Catalysis

Catalysis-Enhancement via Rotary Fluctuation of F_1-ATPase

Rikiya Watanabe, Kumiko Hayashi, Hiroshi Ueno, Hiroyuki Noji[The University of Tokyo]

Biophysical Journal. **105**, 2385–2391 , 2013.

Protein conformational fluctuations modulate the catalytic powers of enzymes. The frequency of conformational fluctuations may modulate the catalytic rate at individual reaction steps. In this study, we modulated the rotary fluctuation frequency of F_1-ATPase (F_1) by attaching probes with different viscous drag coefficients at the rotary shaft of F_1. Individual rotation pauses of F_1 between rotary steps correspond to the waiting state of a certain elementary reaction step of ATP hydrolysis.

Enzyme Catalysis (Cont'd)

Large-scale analysis of the dynamics of enzymes

Dror Tobi[Ariel University]

Proteins: Stru. Fun. & Bioinf., **81**, 1910–1918, 2013.

Protein enzymes enable the cell to execute chemical reactions in short time by accelerating the rate of the reactions in a selective manner. The motions or dynamics of the enzymes are essential for their function. Comparison of the dynamics of a set of 1247 nonhomologous enzymes was performed. For each enzyme, the slowest modes of motion are calculated using the Gaussian network model (GNM) and they are globally aligned. Alignment is done using the dynamic programming algorithm of Needleman and Wunsch, commonly used for sequence alignment.

Insight into the mechanism of aminomutase reaction: A case study of phenylalanine aminomutase by computational approach

Kang Wang, Qianqian Hou, Yongjun Liu [Shandong University]

J. Mol.Graph. and Mod., **46,** 65-73, 2013.

The *Taxus canadensis* phenylalanine aminomutase (*Tc*PAM) catalyze the isomerization of (S)-α-phenylalanine to the (R)-β-isomer. The active site of *Tc*PAM contains the signature 5-methylene-3,5-dihydroimidazol-4-one (MIO) prosthesis, observed in the ammonia lyase class of enzymes. Up to now, there are two plausible mechanisms for these MIO-dependent enzymes, i.e., the amino-MIO adduct mechanism and the Friedel–Crafts-type reaction mechanism. In response to this mechanistic uncertainty, the phenylalanine aminomutase mechanism was investigated by using density functional methods.

Binding Region of Alanopine Dehydrogenase Predicted by Unbiased Molecular Dynamics Simulations of Ligand Diffusion

Holger Gohlke [Heinrich-Heine-University], Ulrike Hergert, Tatu Meyer, Daniel Mulnaes, Manfred K. Grieshaber, Sander H. J. Smits, and Lutz Schmitt

J.Chem. Infor. and Mod. **53**, 2493–2498, 2013.

Opine dehydrogenases catalyze the reductive condensation of pyruvate with L-amino acids. Biochemical characterization of alanopine dehydrogenase from *Arenicola marina* revealed that this enzyme is highly specific for L-alanine. Unbiased molecular dynamics simulations with a homology model of alanopine dehydrogenase captured the binding of L-alanine diffusing from solvent to a putative binding region near a distinct helix-kink-helix motif.

Molecular Dynamics Simulation and Site-Directed Mutagenesis of Alcohol Acyltransferase: A Proposed Mechanism of Catalysis

Luis Morales-Quintana, María Ximena Nuñez-Tobar, María Alejandra Moya-León, and Raúl Herrera [Universidad de Talca]

J.Chem. Infor. and Mod. **53**, 2689–2700, 2013.

Aroma in *Vasconcellea pubescens* fruit is determined by esters, which are the products ofcatalysis by alcohol acyltransferase (VpAAT1). VpAAT1 protein structure displayed the conserved HxxxD motif facing the solvent channel in the center of the structure. To gain insight into the role of these catalytic residues, kinetic and site-directed mutagenesis studies were carried out in VpAAT1 protein. Based on dead-end inhibition studies, the kinetic could be described in terms of a ternary complex mechanism with the H166 residue as the catalytic base. Kinetic results showed the lowest Km value for hexanoyl-CoA.

Enzyme Catalysis (Cont'd)

Release of Halide Ions from the Buried Active Site of the Haloalkane Dehalogenase LinB Revealed by Stopped-Flow Fluorescence Analysis and Free Energy Calculations

Jana Hladilkova, Zbynek Prokop, Radka Chaloupkova, Jiri Damborsky, and Pavel Jungwirth [Masaryk University]

J. Phys. Chem. B., **117**, 14329–14335, 2013**.**

Release of halide ions is an essential step of the catalytic cycle of haloalkane dehalogenases. Here we describe experimentally and computationally the process of release of a halide anion from the buried active site of the haloalkane dehalogenase LinB. Using stopped-flow fluorescence analysis and umbrella sampling free energy calculations, we show that the anion binding is ion-specific and follows the ordering $I^- > Br^- > Cl^-$. We also address the issue of the protonation state of the catalytic His272 residue and its effect on the process of halide release.

Protein-Protein Interactions

Identifying protein complexes from heterogeneous biological data

Min Wu[Institute for Infocomm Research,A*STAR], Zhipeng Xie, Xiaoli Li, Chee-Keong Kwoh and Jie Zheng

Proteins: Stru. Fun. & Bioinf., **81**, 2023–2033, 2013.

With the increasing availability of diverse biological information for proteins, integration of heterogeneous data becomes more useful for many problems in proteomics, such as annotating protein functions, predicting novel protein–protein interactions and so on. We present an integrative approach called InteHC (Integrative Hierarchical Clustering) to identify protein complexes from multiple data sources. Although integrating multiple sources could improve the coverage of current insufficient protein interactome, it could also introduce potential false-positive interactions that could hurt the performance of protein complex prediction.

Two-dimensional replica-exchange method for predicting protein–ligand binding structures

Hironori Kokubo [Takeda Pharmaceutical Co., Ltd.], Toshimasa Tanaka, Yuko Okamoto

J. Comp. Chem., **34**, 2601–2614, 2013.

We have developed a two-dimensional replica-exchange method for the prediction of protein–ligand binding structures. The first dimension is the umbrella sampling along the reaction coordinate, which is the distance between a protein binding pocket and a ligand. The second dimension is the solute tempering, in which the interaction between a ligand and a protein and water is weakened. The second dimension is introduced to make a ligand follow the umbrella potential more easily and enhance the binding events, which should improve the sampling efficiency.

Destabilization of the MutSα's protein-protein interface due to binding to the DNA adduct induced by anticancer agent carboplatin via molecular dynamics simulations

Lacramioara Negureanu, Freddie R. Salsbury Jr [Wake Forest University]

J. Mol.Mod., **19,** 4969-4989, 2013.

DNA mismatch repair (MMR) proteins maintain genetic integrity in all organisms by recognizing and repairing DNA errors. Such alteration of hereditary information can lead to various diseases, including cancer. Besides their role in DNA repair, MMR proteins detect and initiate cellular responses to certain type of DNA damage. This study indicates that strong, specific interactions at the interface of MutSα in response to the mismatched DNA recognition are replaced by weak, non-specific interactions in response to the damaged DNA recognition.

Protein-Protein Interactions (Cont'd)

Conformation Control of Abiotic α-Helical Foldamers

Serge Perato, Jade Fogha, Muriel Sebban, Anne Sophie Voisin-Chiret, Jana Sopkova-de Oliveira Santos[Normandie Université], Hassan Oulyadi, and Sylvain Rault

J.Chem. Infor. and Mod. **53**, 2671–2680, 2013.

A!

With the aim to find new protein–protein inhibitors, a three part methodology was applied to oligophenylpyridines. Theoretical ring twist angle predictions have been validated by X-ray diffraction and molecular dynamics simulations with NMR constraints. Careful choice of substituent and nitrogen positions in oligophenylpyridyl foldamer units opens the way to conformational control of the side chain distribution of this α-helix mimic.

Effective Screening Strategy Using Ensembled Pharmacophore Models Combined with Cascade Docking: Application to p53-MDM2 Interaction Inhibitors

Xin Xue, Jin-Lian Wei, Li-Li Xu, Mei-Yang Xi, Xiao-Li Xu, Fang Liu, Xiao-Ke Guo, Lei Wang, Xiao-Jin Zhang, Ming-Ye Zhang, Meng-Chen Lu, Hao-Peng Sun[China Pharmaceutical University], and Qi-Dong You

J.Chem. Infor. and Mod. **53**, 2715–2729, 2013.

S!

Protein–protein interactions (PPIs) play a crucial role in cellular function and form the backbone of almost all biochemical processes. In recent years, protein–protein interaction inhibitors (PPIIs) have represented a treasure trove of potential new drug targets. Unfortunately, there are few successful drugs of PPIIs on the market. Structure-based pharmacophore (SBP) combined with docking has been demonstrated as a useful Virtual Screening (VS) strategy in drug development projects. However, the combination of target complexity and poor binding affinity prediction has thwarted the application of this strategy in the discovery of PPIIs. Here we report an effective VS strategy on p53-MDM2 PPI.

Fragment-Based Identification of a Locus in the Sec7 Domain of Arno for the Design of Protein–Protein Interaction Inhibitors

Jad Rouhana, Francois Hoh, Sébastien Estaran, Corinne Henriquet, Yvan Boublik, Aziz Kerkour, Romain Trouillard, Jean Martinez, Martine Pugnière, André Padilla, and Alain Chavanieu [Universités Montpellier 1 et 2]

J.Med.Chem., **56,** 8497–8511, 2013.

By virtual screening using a fragment-based drug design (FBDD) approach, 33 fragments were selected within small pockets around interaction hot spots on the Sec7 surface of the nucleotide exchange factor Arno, and then their ability to interfere with the Arno-catalyzed nucleotide exchange on the G-protein Arf1 was evaluated. By use of SPR, NMR, and fluorescence assays, the direct binding of three of the identified fragments to Arno Sec7 domain was demonstrated and the promiscuous aggregate behavior evaluated. Then the binding mode of one fragment and of a more active analogue was solved by X-ray crystallography.

Evolutionary Pressure on the Topology of Protein Interface Interaction Networks

Margaret E. Johnson and Gerhard Hummer [National Institutes of Health, Bethesda]

J. Phys. Chem. B., **117**, 13098–13106, 2013**.**

The densely connected structure of protein–protein interaction (PPI) networks reflects the functional need of proteins to cooperate in cellular processes. However, PPI networks do not adequately capture the competition in protein binding. By contrast, the interface interaction network (IIN) studied here resolves the modular character of protein–protein binding and distinguishes between simultaneous and exclusive interactions that underlie both cooperation and competition. We show that the topology of the IIN is under evolutionary pressure, and we connect topological features of the IIN to specific biological functions.

Membrane Proteins and Lipid Peptide Interactions

Membrane Permeation Induced by Aggregates of Human Islet Amyloid Polypeptides

Chetan Poojari, Dequan Xiao, Victor S. Batista, Birgit Strodel [Heinrich Heine University Düsseldorf]

Biophysical Journal. **105**, 2323–2332, 2013.

Several neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as well as nonneuropathic diseases such as type II diabetes and atrial amyloidosis are associated with aggregation of amyloid polypeptides into fibrillar structures, or plaques. In this study, we use molecular dynamicssimulations to test the stability and orientation of membrane-embedded aggregates of the human islet amyloid polypeptide (hIAPP) implicated in type II diabetes. We find that in both monolayers and bilayers of dipalmitoylphosphatidylglycerol (DPPG) hIAPP trimers and tetramers remain inside the membranes and preserve their β-sheet secondary structure.

Concentration effects of sumatriptan on the properties of model membranes by molecular dynamics simulations

Irene Wood, Mónica Pickholz [Universidad de Buenos Aires]

Euro.biophy. jour., **42**, 833-841, 2013.

In this work, we report a molecular dynamics simulations study of protonated sumatriptan (pSMT) in a fully hydrated bilayer of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidyl-choline at the fluid lamellar phase. The simulations were carried out at three different drug/lipid stoichiometries, 1:75, 1:10 and 1:3, under NPT conditions. Our results show partition of pSMT between the lipid head-water interphase and water phase.

Interaction of Piscidin-1 with zwitterionic versus anionic membranes: a comparative molecular dynamics study

Arezoo Rahmanpour, Mohammad Mehdi Ghahremanpour, Faramarz Mehrnejad[University of Tehran] & Majid Erfani Moghaddam

J. Biomol. Stru. and Dyn., ***31,*** 1393-1403,*2013.*

Understanding the relationship between lipid composition and action of antimicrobial peptides or considering how different lipid bilayers respond to AMPs may help us design more effective peptide drugs in the future. In this contribution, we intend to elucidate how two currently used membrane models, namely palmitoyl-oleoyl-phosphtidylglycerol (POPG) and 1-palmitoyl-oleoyl-glycero-phosphocholine (POPC), respond to antimicrobial peptide Piscidin-1 (Pis-1).

GalaxyDock2: Protein–ligand docking using beta-complex and global optimization

Woong-Hee Shin, Jae-Kwan Kim,Deok-Soo Kim, Chaok Seok [Seoul National University]

J. Comp. Chem., **34**, 2647–2656, 2013.

In this article, an enhanced version of GalaxyDock protein–ligand docking program is introduced. GalaxyDock performs conformational space annealing (CSA) global optimization to find the optimal binding pose of a ligand both in the rigid-receptor mode and the flexible-receptor mode. Binding pose prediction has been improved compared to the earlier version by the efficient generation of high-quality initial conformations for CSA using a predocking method based on a beta-complex derived from the Voronoi diagram of receptor atoms.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Effect of the aminoacid composition of model α-helical peptides on the physical properties of lipid bilayers and peptide conformation: a molecular dynamics simulation

Milan Melicherčík [Comenius University], Alžbeta Holúbeková, Tibor Hianik, Ján Urban

J. Mol.Mod., **19,** 4723-4730 , 2013.

The interaction of a model Lys flanked α-helical peptides K_2-X_{24}-K_2, (X = A,I,L,L+A,V) with lipid bilayers composed of dimyristoylphosphatidylcholine (DMPC) and dipalmitoylphosphatidylcholine (DPPC) both, in a gel and in a liquid-crystalline state, has been studied by molecular dynamics simulations. It has been shown that these peptides cause disordering of the lipid bilayer in the gel state but only small changes have been monitored in a liquid-crystalline state.

A knowledge-based halogen bonding scoring function for predicting protein-ligand interactions

Yingtao Liu, Zhijian Xu, Zhuo Yang, Kaixian Chen, Weiliang Zhu [Chinese Academy of Sciences]

J. Mol.Mod., **19,** 5015-5030, 2013.

S!

Halogen bonding, a non-covalent interaction between the halogen σ-hole and Lewis bases, could not be properly characterized by majority of current scoring functions. In this study, a knowledge-based halogen bonding scoring function, termed XBPMF, was developed by an iterative method for predicting protein-ligand interactions. Three sets of pairwise potentials were derived from two training sets of protein-ligand complexes from the Protein Data Bank.

Training Based on Ligand Efficiency Improves Prediction of Bioactivities of Ligands and Drug Target Proteins in a Machine Learning Approach

Nobuyoshi Sugaya [Drug Discovery Department, Research & Development Division]

J.Chem. Infor. and Mod. **53**, 2525–2537, 2013.

Machine learning methods based on ligand–protein interaction data in bioactivity databases are one of the current strategies for efficiently finding novel lead compounds as the first step in the drug discovery process. Although previous machine learning studies have succeeded in predicting novel ligand–protein interactions with high performance, all of the previous studies to date have been heavily dependent on the simple use of raw bioactivity data of ligand potencies measured by IC_{50}, EC_{50}, K_i, and K_d deposited in databases. ChEMBL provides us with a unique opportunity to investigate whether a machine-learning-based classifier created by reflecting ligand efficiency other than the IC_{50}, EC_{50}, K_i, and K_d values can also offer high predictive performance.

Computation of Binding Energies Including Their Enthalpy and Entropy Components for Protein–Ligand Complexes Using Support Vector Machines

Chaitanya A. K. Koppisetty, Martin Frank, Graham J. L. Kemp, and Per-Georg Nyholm [University of Gothenburg]

J.Chem. Infor. and Mod. **53**, 2559–2570, 2013.

S!

Computing binding energies of protein–ligand complexes including their enthalpy and entropy terms by means of computational methods is an appealing approach for selecting initial hits and for further optimization in early stages of drug discovery. Despite the importance, computational predictions of thermodynamic components have evaded attention and reasonable solutions. In this study, support vector machines are used for developing scoring functions to compute binding energies and their enthalpy and entropy components of protein–ligand complexes.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Recognition in a Diverse Set of Protein–Ligand Interactions Studied with Molecular Dynamics Simulations and End-Point Free Energy Calculations

Bo Wang, Liwei Li, Thomas D. Hurley, and Samy O. Meroueh [Indiana University School of Medicine

J.Chem. Infor. and Mod. **53**, 2659–2670, 2013.

End-point free energy calculations using MM-GBSA and MM-PBSA provide a detailed understanding of molecular recognition in protein–ligand interactions. The binding free energy can be used to rank-order protein–ligand structures in virtual screening for compound or target identification. Here, we carry out free energy calculations for a diverse set of 11 proteins bound to 14 small molecules using extensive explicit-solvent MD simulations. The structure of these complexes was previously solved by crystallography and their binding studied with isothermal titration calorimetry (ITC) data enabling direct comparison to the MM-GBSA and MM-PBSA calculations.

Simulation Study of the Structure and Phase Behavior of Ceramide Bilayers and the Role of Lipid Headgroup Chemistry

Shan Guo, Timothy C. Moore, Christopher R. Iacovella, L. Anderson Strickland, and Clare McCabe [Vanderbilt University]

J. Chem. Theor. and Comp, **9**, 5116-5126, 2013.

Ceramides are known to be a key component of the stratum corneum, the outermost protective layer of the skin that controls barrier function. Here, we propose a modified version of the CHARMM force field for ceramide simulation, which is directly compared to the more commonly used GROMOS-based force field of Berger (*Biophys. J.* **1997**,*72*, 2002–2013); while both force fields are shown to closely match experiment from a structural standpoint at the physiological temperature of skin, the modified CHARMM force field is better able to capture the thermotropic phase transitions observed in experiment.

NBD-Labeled Cholesterol Analogues in Phospholipid Bilayers: Insights from Molecular Dynamics

João R. Robalo, J. P. Prates Ramalho, and Luís M. S. Loura [Universidade de Évora]

J. Phys. Chem. B., **117**, 13731–13742, 2013**.**

Nitrobenzoxadiazole (NBD)-labeled sterols are commonly used as fluorescent cholesterol analogues in membrane biophysics. However, some experimental reports have questioned their ability to emulate the behavior of cholesterol in phospholipid bilayers. For the purpose of a detailed clarification of this matter, atomistic molecular dynamics simulations of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) bilayers, containing either cholesterol or one of two fluorescent cholesterol analogues, 22-NBD-cholesterol or 25-NBD-cholesterol, were carried out.

Protein Folding

Ultrafast folding and molecular dynamics of a linear hydrophobic β-hairpin

Upadhyayula Surya Raghavender [Tata Institute of Fundamental Research]

J. Biomol. Stru. and Dyn., ***31***, 1404-1410,*2013.*

The first computational study of the folding and dynamics of a hydrophobic β-hairpin containing a central heterochiral diproline segment is reported. Linear hydrophobic sequences containing centrally positioned diproline motifs, heterochiral (DL/LD) and homochiral (LL/DD)), are investigated for their ability to form β-hairpins. Heterochiral diproline motifs (LD/DL) reveal the formation of stable β-hairpins with the backbone adopting β-turn conformation and the formation of backbone hydrogen bonds with antiparallel cross-strand registry, whereas the homochiral diproline (LL/DD) containing sequences tend to adopt PP_{II} helix conformation.

How Kinetics within the Unfolded State Affects Protein Folding: An Analysis Based on Markov State Models and an Ultra-Long MD Trajectory

Nan-jie Deng, Wei Dai, and Ronald M. Levy [the State University of New Jersey]

J. Phys. Chem. B., **117**, 12787–12799, 2013**.**

Understanding how kinetics in the unfolded state affects protein folding is a fundamentally important yet less well-understood issue. Here we employ three different models to analyze the unfolded landscape and folding kinetics of the miniprotein Trp-cage. The first is a 208 μs explicit solvent MD simulation from D. E. Shaw Research containing tens of folding events. The second is a Markov state model (MSM-MD) constructed from the same ultralong MD simulation; MSM-MD can be used to generate thousands of folding events.

Atomistic Description of the Folding of a Dimeric Protein

Stefano Piana [D. E. Shaw Research, New York], Kresten Lindorff-Larsen, and David E. Shaw

J. Phys. Chem. B., **117**, 12935-12942, 2013**.**

Equilibrium molecular dynamics simulations are increasingly being used to describe the folding of individual proteins and protein domains at an atomic level of detail. We use equilibrium molecular dynamics simulations with an aggregate simulation length of 4 ms to elucidate key aspects of the folding mechanism, and of the associated free-energy surface, of the Top7-CFr dimer, a 114-amino-acid protein homodimer with a mixed α/β structure. In these simulations, we observed a number of folding and unfolding events. Each folding event was characterized by the assembly of two unfolded Top7-CFr monomers to form a stable, folded dimer.

Sequence-Dependent Base-Stacking Stabilities Guide tRNA Folding Energy Landscapes

Rongzhong Li, Heming W. Ge, and Samuel S. Cho [Wake Forest University]

J. Phys. Chem. B., **117**, 12943-12952, 2013**.**

The folding of bacterial tRNAs with disparate sequences has been observed to proceed in distinct folding mechanisms despite their structural similarity. To explore the folding landscapes of tRNA, we performed ion concentration-dependent coarse-grained TIS model MD simulations of several *E. coli* tRNAs to compare their thermodynamic melting profiles to the classical absorbance spectra of Crothers and co-workers. To independently validate our findings, we also performed atomistic empirical force field MD simulations of tRNAs, and we compared the base-to-base distances from coarse-grained and atomistic MD simulations to empirical base-stacking free energies.

Peptide Folding (Cont'd)

Folding Coupled with Assembly in Split Green Fluorescent Proteins Studied by Structure-based Molecular Simulations

Mashiho Ito, Takeaki Ozawa, and Shoji Takada [Kyoto University]

J. Phys. Chem. B., **117**, 13212–13218, 2013**.**

Split green fluorescent protein (GFP) is a powerful tool for imaging of protein–protein interactions in living cells, but molecular mechanisms of the folding and the assembly of split GFPs are poorly understood. Here, using a simple Go model that is based on the energy landscape theory, we performed comprehensive folding simulations of six split GFPs with different split points. Of the six, the fluorescence recovery was reported in four but not in the other two. In the simulations, we found that when the complete folding and assembly were observed, the N-terminal fragment always folded earlier than the C-terminal fragment.

Binding and Folding of the Small Bacterial Chaperone HdeA

Logan S. Ahlstrom, Alex Dickson, and Charles L. Brooks[The University of Michigan]

J. Phys. Chem. B., **117**, 13219–13225, 2013**.**

The small pH stress-sensing chaperone HdeA helps pathogenic enteric *E. coli* survive passage through the severely acidic environment of the mammalian stomach. Under stress conditions, HdeA transitions from an inactive folded dimer to a chaperone-active unfolded monomer to prevent the acid-induced aggregation of periplasmic proteins. Here we use a topology-based Gō-like model to delineate the relationship between dimer interface formation and monomer folding and to better understand the structural details of the chaperone activation mechanism.

Protein-Nucleic acid Interactions

Kinetics of Allosteric Transitions in *S*-adenosylmethionine Riboswitch Are Accurately Predicted from the Folding Landscape

Jong-Chin Lin and D. Thirumalai [University of Maryland]

J. Am. Chem. Soc., 2013, **135**, 16641–16650

Riboswitches are RNA elements that allosterically regulate gene expression by binding cellular metabolites. The SAM-III riboswitch, one of several classes that binds *S*-adenosylmethionine (SAM), represses translation upon binding SAM (OFF state) by encrypting the ribosome binding sequence. We have carried out simulations of the RNA by applying mechanical force (*f*) to the ends of SAM-III, with and without SAM, to get quantitative insights into the *f*-dependent structural changes.

Cross-talk between the ligand- and DNA-binding domains of estrogen receptor

Wei Huang, Geoffrey L. Greene,Krishnakumar M. Ravikumar , Sichun Yang [Case Western Reserve University]

Proteins: Stru. Fun. & Bioinf., **81**, 1900–1909, 2013.

A!

Estrogen receptor alpha (ERα) is a hormone-responsive transcription factor that contains several discrete functional domains, including a ligand-binding domain (LBD) and a DNA-binding domain (DBD). Despite a wealth of knowledge about the behaviors of individual domains, the molecular mechanisms of cross-talk between LBD and DBD during signal transduction from hormone to DNA-binding of ERα remain elusive. Here, we apply a multiscale approach combining coarse-grained (CG) and atomistically detailed simulations to characterize this cross-talk mechanism via an investigation of the ERα conformational landscape.

Protein – Nucleic acid Interactions (Cont'd)

The study of interactions between DNA and PcrA DNA helicase by using targeted molecular dynamic simulations

Hao Wang [Ningxia Medical University], Jiajia Cui, Wei Hong, Ian C. Paterson, Charles A. Laughton

J. Mol.Mod., **19,** 4997-5006, 2013.

DNA helicases are important enzymes involved in all aspects of nucleic acid metabolism, ranging from DNA replication and repair to recombination, rescue of stalled replication and translation. DNA helicases are molecular motors. Through conformational changes caused by ATP hydrolysis and binding, they move along the template double helix, break the hydrogen bonds between the two strands and separate the template chains, so that the genetic information can be accessed. In this paper, targeted molecular dynamic simulations were performed to study the important interactions between DNA and PcrA DNA helicase, which can not be observed from the crystal structures.

Speed-Selectivity Paradox in the Protein Search for Targets on DNA: Is It Real or Not?

Alex Veksler and Anatoly B. Kolomeisky [Rice University]

J. Phys. Chem. B., **117**, 12695–12701, 2013**.**

Protein search for targets on DNA starts all major biological processes. Although significant experimental and theoretical efforts have been devoted to investigation of these phenomena, mechanisms of protein–DNA interactions during the search remain not fully understood. One of the most surprising observations is known as a speed-selectivity paradox. We developed a discrete-state stochastic approach that allowed us to investigate explicitly target search phenomena and to analyze the speed-selectivity paradox.

Weak Frustration Regulates Sliding and Binding Kinetics on Rugged Protein–DNA Landscapes

Amir Marcovitz and Yaakov Levy[Weizmann Institute of Science]

J. Phys. Chem. B., **117**, 13005-13014, 2013**.**

A fundamental step in gene-regulatory activities, such as repression, transcription, and recombination, is the binding of regulatory DNA-binding proteins (DBPs) to specific targets in the genome. Here, we structurally assessed the interface adopted by a variety of DBPs to bind DNA specifically and nonspecifically, and found that many DBPs utilize one interface to specifically recognize a DNA sequence and another to assist in propagating along the DNA through nonspecific associations.

Nucleic Acids

Modeling Spatial Correlation of DNA Deformation: DNA Allostery in Protein Binding

Xinliang Xu, Hao Ge, Chan Gu, Yi Qin Gao, Siyuan S. Wang, Beng Joo Reginald Thio, James T. Hynes, X. Sunney Xie, and Jianshu Cao

J. Phys. Chem. B., **117**, 13378–13387, 2013**.**

We report a study of DNA deformations using a coarse-grained mechanical model and quantitatively interpret the allosteric effects in protein–DNA binding affinity. A recent single-molecule study (Kim et al. *Science* **2013**, *339*, 816) showed that when a DNA molecule is deformed by specific binding of a protein, the binding affinity of a second protein separated from the first protein is altered. Experimental observations together with molecular dynamics simulations suggested that the origin of the DNA allostery is related to the observed deformation of DNA's structure, in particular, the major groove width.

Surfaces, Catalysts, and Materials Subjects

Ab Initio molecular dynamics study of ethylene adsorption onto Si(001) surface: Short-time fourier transform analysis of structural coordinate autocorrelation function

Yung Ting Lee, Jyh Shing Lin [Tamkang University]

J. Comp. Chem., **34**, 2697–2706, 2013.

The reaction dynamics of ethylene adsorption onto the Si(001) surface have been studied by combining density functional theory-based molecular dynamics simulations with molecular adsorption sampling scheme for investigating all kinds of reaction pathways and corresponding populations. Based on the calculated results, three possible reaction pathways—the indirect adsorption, the direct adsorption, and the repelling reaction—have been found. First, the indirect adsorption, in which the ethylene ($C_2H_{4(ads)}$) forms the π-bonded $C_2H_{4(ads)}$ with the buckled-down Si atom to adsorb on the Si(001) surface and then turns into the di-σ-bonded $C_2H_{4(ads)}$, is the major reaction pathway.

Comparison of the capillary wave method and pressure tensor route for calculation of interfacial tension in molecular dynamics simulations

Stella Nickerson, Denzil S. Frost,Harrison Phelan, Lenore L. Dai [Arizona State University]

J. Comp. Chem., **34**, 2707–2715, 2013.

We have studied the calculation of surface and interfacial tension for a variety of liquid–vapor and liquid–liquid interfaces using molecular dynamics (MD) simulations. Because of the inherently small scale of MD systems, large pressure fluctuations can cause imprecise calculations of surface tension using the pressure tensor route. The capillary wave method exhibited improved precision and stability throughout all of the simulated systems in this study.

2. METHODOLOGY

Quantitative Structure-Activity Relations

HomoSAR: Bridging comparative protein modeling with quantitative structural activity relationship to design new peptides

Mahesh R. Borkar, Raghuvir R. S. Pissurlenkar, Evans C. Coutinho [Bombay College of Pharmacy]

J. Comp. Chem., **34**, 2635–2646, 2013.

Peptides play significant roles in the biological world. To optimize activity for a specific therapeutic target, peptide library synthesis is inevitable; which is a time consuming and expensive. Computational approaches provide a promising way to simply elucidate the structural basis in the design of new peptides. Earlier, we proposed a novel methodology termed *HomoSAR* to gain insight into the structure activity relationships underlying peptides. Based on an integrated approach, *HomoSAR* uses the principles of homology modeling in conjunction with the quantitative structural activity relationship formalism to predict and design new peptide sequences with the optimum activity.

Quantitative Structure-Activity Relations (Cont'd)

Combining structure- and ligand-based approaches for studies of interactions between different conformations of the hERG K^+ channel pore and known ligands

Alessio Coi, Anna Maria Bianucci [INSTM (Consorzio National Interuniversity Consortium of Materials Science and Technology)]

J. Mol.Graph. and Mod., **46,** 93-104, 2013.

Drug-induced insurgence of cardiotoxic effects signaled by the prolongation of the QT interval in the electrocardiogram, has the potential to evolve into a characteristic arrhythmic event named Torsade de Pointes (TdP). Although several different mechanisms can theoretically lead to prolonged QT interval, most of drugs showing this side effect, prolong the cardiac repolarization time through the inhibition of the rapid component of the delayed repolarizing current (I_{Kr}) which in humans is carried by a K^+ channel protein encoded by hERG. In this study, four 3D-models, representing different conformational states of hERG K^+channel, were built by a homology-based technique.

2D, 3D-QSAR and molecular docking of 4(1*H*)-quinolones analogues with antimalarial activities

Thulie Paulinne Jiménez Villalobos, Ricardo Gaitán Ibarra, Joel José Montalvo Acosta [University of Cartagena]

J. Mol.Graph. and Mod., **46,** 105-124, 2013.

Cytochrome bc_1 has become a major focus as a molecular target in malaria parasites, which are the most important vector-borne infectious disease in the world. The inhibition of cytochrome bc_1 blocks the mitochondrial respiratory chain and the consequent arrest of pyrimidine biosynthesis, which is essential for parasite development. The authors developed a theoretical study of two-dimensional, three-dimensional quantitative structure–activity relationships and a docking analysis of a series of 4(1*H*)-quinolones acting as cytochrome bc_1 inhibitors.

Pre-processing Feature Selection for Improved C&RT Models for Oral Absorption

Danielle Newby, Alex. A. Freitas, and Taravat Ghafourian [Tabriz University of Medical Sciences]

J.Chem. Infor. and Mod. **53**, 2730–2742, 2013.

There are currently thousands of molecular descriptors that can be calculated to represent a chemical compound. Utilizing all molecular descriptors in Quantitative Structure–Activity Relationships (QSAR) modeling can result in overfitting, decreased interpretability, and thus reduced model performance. In this work we compare two broad approaches for feature selection: (1) a "two-stage" feature selection procedure, where a pre-processing feature selection method selects a subset of descriptors, and then classification and regression trees (C&RT) selects descriptors from this subset to build a decision tree; (2) a "one-stage" approach where C&RT is used as the only feature selection technique.

How to Deal with Low-Resolution Target Structures: Using SAR, Ensemble Docking, Hydropathic Analysis, and 3D-QSAR to Definitively Map the αβ-Tubulin Colchicine Site

Chenxiao Da, Susan L. Mooberry, John T. Gupton, and Glen E. Kellogg [Virginia Commonwealth University]

J.Med.Chem., **56,** 7382–7395, 2013.

αβ-Tubulin colchicine site inhibitors (CSIs) from four scaffolds that we previously tested for antiproliferative activity were modeled to better understand their effect on microtubules. Docking models, constructed by exploiting the SAR of a pyrrole subset and HINT scoring, guided ensemble docking of all 59 compounds. This conformation set and two variants having progressively less structure knowledge were subjected to CoMFA, CoMFA+HINT, and CoMSIA 3D-QSAR analyses.

Potentials and Parameters

Rapid Calculation of Accurate Atomic Charges for Proteins via the Electronegativity Equalization Method

Crina-Maria Ionescu, Stanislav Geidl, Radka Svobodová Vařeková[Masaryk University Brno], and Jaroslav Koča

J.Chem. Infor. and Mod. **53**, 2548–2558, 2013.

We focused on the parametrization and evaluation of empirical models for fast and accurate calculation of conformationally dependent atomic charges in proteins. The models were based on the electronegativity equalization method (EEM), and the parametrization procedure was tailored to proteins. We used large protein fragments as reference structures and fitted the EEM model parameters using atomic charges computed by three population analyses (Mulliken, Natural, iterative Hirshfeld), at the Hartree–Fock level with two basis sets (6-31G*, 6-31G**) and in two environments (gas phase, implicit solvation).

Using Multistate Reweighting to Rapidly and Efficiently Explore Molecular Simulation Parameters Space for Nonbonded Interactions

Himanshu Paliwal and Michael R. Shirts [University of Virginia]

J. Chem. Theor. and Comp, **9**, 4700–4717, 2013.

Multistate reweighting methods such as the multistate Bennett acceptance ratio (MBAR) can predict free energies and expectation values of thermodynamic observables at poorly sampled or unsampled thermodynamic states using simulations performed at only a few sampled states combined with single point energy reevaluations of these samples at the unsampled states. In this study, we demonstrate the power of this general reweighting formalism by exploring the effect of simulation parameters controlling Coulomb and Lennard-Jones cutoffs on free energy calculations and other observables.

Molecular Dynamics

All-Atom Molecular Dynamics Simulation of Photosystem II Embedded in Thylakoid Membrane

Koji Ogata, Taichi Yuki, Makoto Hatakeyama, Waka Uchida, and Shinichiro Nakamura [Tokyo Institute of Technology]

J. Am. Chem. Soc., 2013, **135**, 15670–15673

The molecular dynamics simulation is reported. The latest data on photosystem II structure, a thylakoid membrane model with the same lipid class distribution and fatty acid composition as the native thylakoid membrane, are used. The results indicate that the transfer of water, oxygen and protons has different pathways. The root mean square (rms)-fluctuation analysis of trajectory revealed that the residues surrounding the oxygen-evolving center (OEC) show small fluctuations and that most of the water molecules there show large fluctuation and are on proposed pathways for water and oxygen transfer.

Molecular Dynamics (Cont'd)

Energetics of Multi-Ion Conduction Pathways in Potassium Ion Channels

Philip W. Fowler, Enrique Abad, Oliver Beckstein, and Mark S. P. Sansom [University of Oxford]

J. Chem. Theor. and Comp, **9**, 5176–5189, 2013.

Potassium ion channels form pores in cell membranes, allowing potassium ions through while preventing the passage of sodium ions. Despite numerous high-resolution structures, it is not yet possible to relate their structure to their single molecule function other than at a qualitative level. Over the past decade, there has been a concerted effort using molecular dynamics to capture the thermodynamics and kinetics of conduction by calculating potentials of mean force (PMF). Here, we calculate seven independent PMFs, thereby studying the differences between two potassium ion channels, the effect of the CHARMM CMAP forcefield correction, and the sensitivity and reproducibility of the method.

Rapid Exploration of Configuration Space with Diffusion-Map-Directed Molecular Dynamics

Wenwei Zheng , Mary A. Rohrdanz , and Cecilia Clementi [Rice University]

J. Phys. Chem. B., **117**, **12769–12776**, 2013**.**

The gap between the time scale of interesting behavior in macromolecular systems and that which our computational resources can afford often limits molecular dynamics (MD) from understanding experimental results and predicting what is inaccessible in experiments. In this paper, we introduce a new sampling scheme, named diffusion-map-directed MD (DM-d-MD), to rapidly explore molecular configuration space. The method uses a diffusion map to guide MD on the fly. DM-d-MD can be combined with other methods to reconstruct the equilibrium free energy, and here, we used umbrella sampling as an example.

Ion Permeation in the NanC Porin from Escherichia coli: Free Energy Calculations along Pathways Identified by Coarse-Grain Simulations

Jens Dreyer, Paul Strodel, Emiliano Ippoliti, Justin Finnerty, Bob Eisenberg, and Paolo Carloni

J. Phys. Chem. B., **117**, 13534–13542, 2013**.**

Using the X-ray structure of a recently discovered bacterial protein, the *N*-acetylneuraminic acid-inducible channel (NanC), we investigate computationally K^+ and Cl^- ions' permeation. We identify ion permeation pathways that are likely to be populated using coarse-grain Monte Carlo simulations. Next, we use these pathways as reaction coordinates for umbrella sampling-based free energy simulations. We find distinct tubelike pathways connecting specific binding sites for K^+ and, more pronounced, for Cl^- ions. Both ions permeate the porin preserving almost all of their first hydration shell.

A Structural Study of Ion Permeation in OmpF Porin from Anomalous X-ray Diffraction and Molecular Dynamics Simulations

Balasundaresan Dhakshnamoorthy, Brigitte K. Ziervogel, Lydia Blachowicz, and Benoît Roux [University of Chicago Chicago]

J. Am. Chem. Soc., 2013, **135**, 16561–16568

OmpF, a multiionic porin from *Escherichia coli*, is a useful protypical model system for addressing general questions about electrostatic interactions in the confinement of an aqueous molecular pore. Here, favorable anion locations in the OmpF pore were mapped by anomalous X-ray scattering of Br^- ions from four different crystal structures and compared with Mg^{2+} sites and Rb^+ sites from a previous anomalous diffraction study to provide a complete picture of cation and anion transfer paths along the OmpF channel.

Molecular Dynamics (Cont'd)

Hamiltonian replica-permutation method and its applications to an alanine dipeptide and amyloid-β(29–42) peptides

Satoru G. Itoh [Institute for Molecular Science, Okazaki] and Hisashi Okumura

J. Comp. Chem., **34**, 2493–2497, 2013.

We propose the Hamiltonian replica-permutation method (RPM) (or multidimensional RPM) for molecular dynamics and Monte Carlo simulations, in which parameters in the Hamiltonian are permuted among more than two replicas with the Suwa-Todo algorithm. We apply the Coulomb RPM, which is one of realization of the Hamiltonian RPM, to an alanine dipeptide and to two amyloid-β(29–42) molecules.

Characterization of the polymorphic states of copper(II)-bound Aβ(1–16) peptides by computational simulations

Liang Xu [Dalian University of Technology], Xiaojuan Wang, Shengsheng Shan and Xicheng Wang

J. Comp. Chem., **34**, 2524–2536, 2013.

Understanding the polymorphic states of metal amyloid β (Aβ) interactions helps to elucidate metal-mediated events in the pathogenesis of Alzheimer's disease. Systematic investigations on the effects of metal ions such as Cu^{2+} and Zn^{2+} on the structural and thermodynamic properties of Aβ at the molecular lever seem desirable. In this study, a set of new AMBER force field parameters was developed to model various Cu^{2+} coordination spheres of Aβ. These parameters including force constants and partial charges obtained using restrained electrostatic potential method were then validated in replica-exchange molecular dynamics simulations on six Cu^{2+}-Aβ(1–16) systems.

DFT and docking studies of rhodostreptomycins A and B and their interactions with solvated/nonsolvated Mg^{2+} and Ca^{2+} ions

Christiaan Jardínez, Ines Nicolás-Vázquez, Julian Cruz-Borbolla[Unidad Universitaria], Cesar A. González-Ramírez,Miguel Cepeda, Jose Correa-Basurto, Thangarasu Pandiyan, Rene Miranda

J. Mol.Mod., **19,** 4823-4836, 2013.

The interactions of L-aminoglucosidic stereoisomers such as rhodostreptomycins A (Rho A) and B (Rho B) with cations (Mg^{2+}, Ca^{2+}, and H^{+}) were studied by a quantum mechanical method that utilized DFT with B3LYP/6-311G**. Docking studies were also carried out in order to explore the surface recognition properties of L-aminoglucoside with respect to Mg^{2+} and Ca^{2+} ions under solvated and nonsolvated conditions. Although both of the stereoisomers possess similar physicochemical/antibiotic properties against *Helicobacter pylori*, the thermochemical values for these complexes showed that its high affinity for Mg^{2+} cations caused the hydration of Rho B.

Free Energy Perturbation

Modulation of a Protein Free-Energy Landscape by Circular Permutation

Gaël Radou, Marta Enciso, Sergei Krivov, and Emanuele Paci [University of Leeds]

J. Phys. Chem. B., **117**, 13743–13747, 2013**.**

Circular permutations usually retain the native structure and function of a protein while inevitably perturbing its folding dynamics. Using simulations with a structure-based model and a methodology to determine free-energy surfaces from trajectories, we evaluate the effect of a circular permutation on the free-energy landscape of the protein T4 lysozyme. We observe changes which, although subtle, largely affect the cooperativity between the two subdomains. Such a change in cooperativity has been previously experimentally observed and recently also characterized using single molecule optical tweezers and the Crooks relation.

QM and QM/MM

Atomistic understanding of the C·T mismatched DNA base pair tautomerization via the DPT: QM and QTAIM computational approaches

Ol'ha O. Brovarets, Dmytro M. Hovorun [National Academy of Sciences of Ukraine]

J. Comp. Chem., **34**, 2577–2590, 2013.

It was established that the cytosine·thymine (C·T) mismatched DNA base pair with *cis*-oriented N1H glycosidic bonds has propeller-like structure (|N3C4C4N3| = 38.4°), which is stabilized by three specific intermolecular interactions–two antiparallel N4H…O4 (5.19 kcal mol^{-1}) and N3H…N3 (6.33 kcal mol^{-1}) H-bonds and a van der Waals (vdW) contact O2…O2 (0.32 kcal mol^{-1}). It was shown that the C·T ↔ C*·T* tautomerization via the double proton transfer (DPT) is assisted by the O2…O2 vdW contact along the entire range of the intrinsic reaction coordinate (IRC).

Molecular modeling for Cu(II)-aminopolycarboxylate complexes: Structures, conformational energies, and ligand binding affinities

Marina Ćendić, Zoran D. Matović, Robert J. Deeth [University of Kragujevac]

J. Comp. Chem., **34**, 2687–2696, 2013.

A ligand field molecular mechanics (LFMM) force field (FF) has been developed for d^9 copper(II) complexes of aminopolycarboxylate ligands. Training data were derived from DFT geometry optimizations of 14 complexes comprising potentially hexadentate N_2O_4, tetrasubstituted ethylenediamine (ed), and propylenediamine cores with various combinations of acetate and propionate side arms. The FF was validated against 13 experimental structures from X-ray crystallography including hexadentate N_2O_4donors where the nitrogens donors are forced to be *cis* and bis-tridentate ONO ligands which generate complexes with *trans* nitrogen donors.

Can Satraplatin be hydrated before the reduction process occurs? The DFT computational study

Ondřej Bradáč, Tomáš Zimmermann, Jaroslav V. BurdaPages [Charles University]

J. Mol.Mod., **19,** 4669-4680, 2013.

Hydration reactions of two anticancer Pt(IV) complexes JM149 and JM216 (Satraplatin) were studied computationally together with the hydration of the Pt(II) complex JM118, which is a product of the Satraplatin reduction. Thermodynamic and kinetic parameters of the reactions were determined at the B3LYP/6-311++G(2df.2pd)//B3LYP/6-31 + G(d)) level of theory. The water solution was modeled using the COSMO implicit solvation model, with cavities constructed using Klamt's atomic radii.

Simulation of Adsorption Processes at Metallic Interfaces: An Image Charge Augmented QM/MM Approach

Dorothea Golze, Marcella Iannuzzi, Manh-Thuong Nguyen, Daniele Passerone, and Jürg Hutter

J. Chem. Theor. and Comp, **9**, 5086–5097, 2013.

A novel method for including polarization effects within hybrid QM/MM simulations of adsorbate-metal systems is presented. The interactions between adsorbate (QM) and metallic substrate (MM) are described at the MM level of theory. Induction effects are additionally accounted for by applying the image charge formulation. The charge distribution induced within the metallic substrate is modeled by a set of Gaussian charges (image charges) centered at the metal atoms. The image charges and the electrostatic response of the QM potential are determined self-consistently by imposing the constant-potential condition within the metal.

QM and QM/MM (Cont'd)

Quantifying the Mechanism of Phosphate Monoester Hydrolysis in Aqueous Solution by Evaluating the Relevant Ab Initio QM/MM Free-Energy Surfaces

Nikolay V. Plotnikov, B. Ram Prasad, Suman Chakrabarty, Zhen T. Chu, and Arieh Warshel[University of Southern California]

J. Phys. Chem. B., **117**, 12807–12819, 2013**.**

This issue has been explored before by energy minimization with implicit solvent models and by nonsystematic QM/MM energy minimization, as well as by nonsystematic free-energy mapping. However, no study has provided the needed reliable 2D (3D) surfaces that are necessary for reaching concrete conclusions. Here we report a systematic evaluation of the 2D (3D) free-energy maps for several relevant systems, comparing the results of QM(ai)/MM and QM(ai)/implicit solvent surfaces, and provide an advanced description of the relevant energetics. It is found that the 1W path for the hydrolysis of the methyl diphosphate (MDP) trianion is 6–9 kcal/mol higher than that the 2W path.

Fundamental Reaction Pathway for Peptide Metabolism by Proteasome: Insights from First-Principles Quantum Mechanical/Molecular Mechanical Free Energy Calculations

Donghui Wei, Lei Fang, Mingsheng Tang, and Chang-Guo Zhan[University of Kentucky]

J. Phys. Chem. B., **117**, 13418–13434, 2013**.**

Proteasome is the major component of the crucial non-lysosomal protein degradation pathway in the cells, but the detailed reaction pathway is unclear. In this study, first-principles quantum mechanical/molecular mechanical free energy calculations have been performed to explore, for the first time, possible reaction pathways for proteasomal proteolysis/hydrolysis of a representative peptide, succinyl-leucyl-leucyl-valyl-tyrosyl-7-amino-4-methylcoumarin (Suc-LLVY-AMC). The computational results reveal that the most favorable reaction pathway consists of six steps.

Thermal Isomerization of the Chromoprotein asFP595 and Its Kindling Mutant A143G: QM/MM Molecular Dynamics Simulations

Vladimir A. Mironov[M.V. Lomonosov Moscow State University], Maria G. Khrenova, Bella L. Grigorenko, Alexander P. Savitsky, and Alexander V. Nemukhin

J. Phys. Chem. B., **117**, 13507–13514, 2013**.**

We report the results of computational studies of the *trans–cis* isomerization of the anionic and neutral chromophore inside the protein matrices in the ground electronic state for both variants, asFP595 and KFP. Corresponding free energy profiles (potentials of mean force) were evaluated by using molecular dynamics simulations with the quantum mechanical – molecular mechanical (QM/MM) forces. The computed free energy barrier for the *cis–trans*ground state (thermal) isomerization reaction is about 2 kcal/mol higher in KFP than that in asFP595.

On the Photophysics of Carotenoids: A Multireference DFT Study of Peridinin

Stefan Knecht[University of Southern Denmark], Christel M. Marian, Jacob Kongsted, and Benedetta Mennucci

J. Phys. Chem. B., **117**, 13808–13815, 2013**.**

We present a quantum-mechanical investigation of the photophysics of a specific carotenoid, peridinin, which is present in light-harvesting complexes. The fundamental role played by the geometry in determining the position and character of its low-lying singlet electronic states is investigated using a multireference DFT approach in combination with a continuum solvation model. The main photophysical properties of peridinin appear to be governed by the lowest two singlet excited states, as no evidence points to an intermediate S* state and the energies of the upper excited states are too high to allow their population with excitation in the visible range.

Comparative or Homology Modeling

Infernal 1.1: 100-fold faster RNA homology searches

Eric P. Nawrocki [HHMI Janelia Farm Research Campus] and Sean R. Eddy

Bioinformatics. **29**, 2933-2935, 2013.

Infernal builds probabilistic profiles of the sequence andsecondary structure of an RNA family called covariance models (CMs) from structurally annotated multiple sequence alignments given as input. Infernal uses CMs to search for new family members in sequence databases and to create potentially large multiple sequence alignments. Version 1.1 of Infernal introduces a new filter pipeline for RNA homology search based on accelerated profile hidden Markov model (HMM) methods and HMM-banded CM alignment methods.

Associations between the Rho kinase-1 catalytic and PH domain regulatory unit

John W. Craft Jr., Hua Zhang, Marc N. Charendoff, Jeffery T. Mindrebo, Robert J. Schwartz [University of Houston], James M. Briggs

J. Mol.Graph. and Mod., **46,** 74-82, 2013.

Rho-associated kinase, or ROCK, is an important mediator of ventricular remodeling in cardiac hypertrophy. It has a kinase catalytic domain, a coiled–coil domain and a Pleckstrin-Homology domain (PH domain) with a C1 domain insert. The C-terminal region including the PH domain and C1 domain insert is involved in an autoregulatory role for ROCK. We sought to evaluate whether a self association complex could form using computational docking approaches.

Regulation of the transient receptor potential channel TRPA1 by its N-terminal ankyrin repeat domain

Vasilina Zayats, Abdul Samad, Babak Minofar, Katherine E. Roelofs, Thomas Stockner[Medical University Vienna] , Rudiger Ettrich]

J. Mol.Mod., **19,** 4689-4700, 2013.

The transient receptor potential channel A1 (TRPA1) is unique among ion channels of higher vertebrates in that it harbors a large ankyrin repeat domain. The TRPA1 channel is expressed in the inner ear and in nociceptive neurons. It is involved in hearing as well as in the perception of pungent and irritant chemicals. The ankyrin repeat domain has special mechanical properties, which allows it to function as a soft spring that can be extended over a large range while maintaining structural integrity. A calcium-binding site has been experimentally identified within the ankyrin repeats. We built a model of the N-terminal 17 ankyrin repeat structure, including the calcium-binding EF-hand.

Molecular basis of lateral force spectroscopy nano-diagnostics: computational unbinding of autism related chemokine MCP-1 from IgG antibody

Anna Gogolinska, Wieslaw Nowak [Nicolaus Copernicus University]

J. Mol.Mod., **19,** 4773-4780, 2013.

Monocyte-chemoattractant protein-1 (MCP-1), also known as CCL2, is a potent chemoattractant of T cells and monocytes, involved in inflammatory and angio-proliferative brain and retinal diseases. Higher expression of MCP-1 is observed in metastatic tumors. Unusual levels of MCP-1 in the brain may be correlated with autism. In this paper the stability of the medically important MCP-1- immunoglobulin G antibody Fab fragment complex has been studied using steered molecular dynamics (SMD) computer simulations with the aim to model possible arrangements of nano-diagnostics experiments.

Comparative or Homology Modeling (Cont'd)

Molecular interactions between fenoterol stereoisomers and derivatives and the β_2-adrenergic receptor binding site studied by docking and molecular dynamics simulations

Anita Plazinska, Michal Kolinski, Irving W. Wainer, Krzysztof Jozwiak [Medical University of Lublin]

J. Mol.Mod., **19,** 4919-4930, 2013.

The β_2 adrenergic receptor (β_2-AR) has become a model system for studying the ligand recognition process and mechanism of the G protein coupled receptors activation. In the present study stereoisomers of fenoterol and some of its derivatives ($N = 94$ molecules) were used as molecular probes to identify differences in stereo-recognition interactions between β_2-AR and structurally similar agonists. The present study aimed at determining the 3D molecular models of the fenoterol derivative-β_2-AR complexes.

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3. J O U R N A L R E V I E W S

Journal of Molecular Graphics and Modelling, 46, November 2013.

1-9 **Multi-conformation dynamic pharmacophore modeling of the peroxisome proliferator-activated receptor γ for the discovery of novel agonists** ,Young-sik Sohn, Chanin Park, Yuno Lee, Songmi Kim, Sundarapandian Thangapandian, Yongseong Kim, Hyong-Ha Kim, Jung-Keun Suh, Keun Woo Lee [Gyeongsang National University (GNU)]

See Applications / Medicinal Chemmistry and Drug Design.

10-21 **Binding of modulators to mouse and human multidrug resistance P-glycoprotein. A computational study** Gabriel E. Jara, D. Mariano A. Vera [Universidad Nacional de Mar del Plata], Adriana B. Pierini

See Applications / Ligand Binding.

22-28 **Probing the influence of solvent effect on the lithium ion binding affinity of 12-crown-O_3N derivatives with unsaturated side arms: A computational study** ,Rajesh Patidar, Parimal Paul, Bishwajit Ganguly [CSIR-Central Salt & Marine Chemicals Research Institute]

We have investigated employing quantum chemical calculations the stable conformations of 12-crown-O3 N derivatives with unsaturated side-arms and its corresponding Li^+ ion complexation in low polar to high polar solvent medium.

41-51 **Could MM-GBSA be accurate enough for calculation of absolute protein/ligand binding free energies?** Chandrika Mulakala [Jubilant Biosys Limited], Vellarkad N. Viswanadhan

See Applications / Free Energy Perturbations.

52-58 **Conformational preference of glycinamide in solution: An answer derived from combined experimental and computational studies** ,Bishwajit Ganguly [(Council of Scientific and Industrial Research) Bhavnagar], Manoj K. Kesharwani, Nikola Basarić, Eringathodi Suresh, Abul Kalam Biswas, Kata Mlinarić-Majerski

Conformational problems are often subtle but very important in controlling many intricate features in chemistry and biochemistry. We have performed the conformational analysis of glycinamide using NMR experiments and computational studies.

59-64 **Theoretical exploration to second-order nonlinear optical properties of new hybrid complexes via coordination interaction between (metallo)porphyrin and $[MSiW_{11}O_{39}]^{3-}$ ($M = Nb^V$ or V^V) polyoxometalates** ,Ting Zhang, Nana Ma, Likai Yan [Northeast Normal University], Shizheng Wen, Tengying Ma, Zhongmin Su

The second-order nonlinear optical (NLO) properties of hybrid complexes via coordination interaction between porphyrin and Keggin-type polyoxometalates (POMs) α-$[MSiW_{11}O_{39}]^{3-}$ ($M = Nb^V$ or V^V) are investigated by time-dependent density functional theory (TDDFT).

65-73 **Insight into the mechanism of aminomutase reaction: A case study of phenylalanine aminomutase by computational approach** ,Kang Wang, Qianqian Hou, Yongjun Liu [Shandong University]

See Applications / Enzyme Catalysis.

74-82 **Associations between the Rho kinase-1 catalytic and PH domain regulatory unit** ,John W. Craft Jr., Hua Zhang, Marc N. Charendoff, Jeffery T. Mindrebo, Robert J. Schwartz [University of Houston], James M. Briggs

See Methodology / Homology Modeling.

83-92 **Stepwise design of non-covalent wrapping of large diameter carbon nanotubes by peptides** ,Xin Chen [Henan University], Xiaohan Yu, Yafang Liu, Jinglai Zhang

See Applications / Carbon Nanotubes.

93-104 **Combining structure- and ligand-based approaches for studies of interactions between different conformations of the hERG K^+ channel pore and known ligands** ,Alessio Coi, Anna Maria Bianucci [INSTM (Consorzio National Interuniversity Consortium of Materials Science and Technology)]

See Methodology / QSAR.

105-124 **2D, 3D-QSAR and molecular docking of 4(1*H*)-quinolones analogues with antimalarial activities** ,Thulie Paulinne Jiménez Villalobos, Ricardo Gaitán Ibarra, Joel José Montalvo Acosta [University of Cartagena]

See Methodology / QSAR.

Journal of Computational Chemistry, 34 (29), November 2013.

2493–2497 **Hamiltonian replica-permutation method and its applications to an alanine dipeptide and amyloid-β(29–42) peptides** ,Satoru G. Itoh [Institute for Molecular Science, Okazaki] and Hisashi Okumura

See Methodology / Molecular Dynamics.

2498–2501 **Chemically intuitive indices for charge-transfer excitation based on SAC-CI and TD-DFT calculations ,**Masahiro Ehara [Institute for Molecular Science and Research Center for Computational Science], Ryoichi Fukuda,Carlo Adamo, Ilaria Ciofini

A recently proposed charge-transfer (CT) index and some related quantities aimed to the description of CT excitations in push–pull donor–acceptor model systems were computed in vacuum and in ethanol by the direct symmetry-adapted cluster-configuration interaction (SAC-CI) method including solvent effects by means of the nonequilibrium state-specific approach.

Auxiliary basis functions for second-order Møller–Plesset perturbation theory with resolution-of-identity approximation (RI-MP2) are developed for first-, second-, and third-row elements, which are suitable for Pople-type 6-31G** and 6-311G** basis sets.

Journal of Computational Chemistry, 34 (30), November 2013.

2577–2590 **Atomistic understanding of the C·T mismatched DNA base pair tautomerization via the DPT: QM and QTAIM computational approaches ,**Ol'ha O. Brovarets, Dmytro M. Hovorun [National Academy of Sciences of Ukraine]

See Methodology / QM and QM/MM.

2591–2600 **Stochastic structure determination for conformationally flexible heterogenous molecular clusters: Application to ionic liquids ,**Matthew A. Addicoat [Nagoya University] , Syou Fukuoka, Alister J. Page, Stephan Irle

We present a novel method that enables accurate and efficient computational determination of conformationally flexible clusters, "Kick^3" This method uses stochastically generated structures in combination with fast quantum mechanical methods.

2601–2614 **Two-dimensional replica-exchange method for predicting protein–ligand binding structures** Hironori Kokubo [Takeda Pharmaceutical Co., Ltd.],Toshimasa Tanaka, Yuko Okamoto

See Applications / Protein-Nucleic acids.

2615–2624 **Molecular dynamics simulation of benzene in graphite and amorphous carbon slit pores ,**Yu. D. Fomin [Institure for High Pressure Physics Russian Academy of Science (HPPI RAS) 142190]

It is well known that confining a liquid into a pore strongly alters the liquid behavior. Investigations of the effect of confinement are of great importance for many scientific and technological applications. Here, we present a study of the behavior of benzene confined in carbon slit pores.

2625–2634 **Splitting multiple bonds: A comparison of methodologies on the accuracy of bond dissociation energies ,**David Robinson [University of Nottingham]

A benchmarking of different quantum chemical methodologies for the splitting of multiply bonded systems is presented, with an emphasis on quantitative reproduction of experimentally determined dissociation energies. New benchmark full configuration interaction (FCI) calculations are presented for nitrogen and acetylene, and comparisons are made between various methods with both the FCI results and with experiment in an effort to understand qualitatively and quantitatively how well these different methods cope with the bond-breaking process.

2635–2646 **HomoSAR: Bridging comparative protein modeling with quantitative structural activity relationship to design new peptides ,**Mahesh R. Borkar, Raghuvir R. S. Pissurlenkar, Evans C. Coutinho [Bombay College of Pharmacy]

See Applications / Homology Modeling.

2647–2656 **GalaxyDock2: Protein–ligand docking using beta-complex and global optimization ,**Woong-Hee Shin, Jae-Kwan Kim,Deok-Soo Kim, Chaok Seok [Seoul National University]

See Applications / Protein-Nucleic acids.

2657–2665 **A new module for constrained multi-fragment geometry optimization in internal coordinates implemented in the MOLCAS package ,**Victor P. Vysotskiy [Lund University], Jonas Boström,Valera Veryazov

A parallel procedure for an effective optimization of relative position and orientation between two or more fragments has been implemented in the MOLCAS program package. By design, the procedure does not perturb the electronic structure of a system under the study.

Journal of Computational Chemistry, 34 (31), November 2013.

2668–2676 **A high-level *ab initio* study of the N_2 + N_2 reaction channel ,**Leonardo Pacifici [University of Perugia], Marco Verdicchio,Noelia Faginas Lago, Andrea Lombardi,Alessandro Costantini

A new six-dimensional (6D) global potential energy surface (PES) is proposed for the full range description of the interaction of the $N_2(1\Sigma_g^+)+N_2(1\Sigma_g^+)$ system governing collisional processes, including N atom exchange. The related potential energy values were determined using high-level *ab initio* methods.

2677–2686 **The F130L mutation in streptavidin reduces its binding affinity to biotin through electronic polarization effect ,**Juan Zeng, Xiangyu Jia, John Z. H. Zhang , Ye Mei [East China Normal University]

In this work, we carry out molecular dynamics simulations and apply an end-state free energy method to calculate the binding free energies of biotin to wild type streptavidin and its F130L mutant. The absolute binding affinities based on AMBER charge are repulsive, and the mutation induced binding loss is underestimated.

2687–2696 **Molecular modeling for Cu(II)-aminopolycarboxylate complexes: Structures, conformational energies, and ligand binding affinities ,**Marina Ćendić, Zoran D. Matović, Robert J. Deeth [University of Kragujevac]

See Methodology / QM and QM/MM.

2697–2706 ***Ab Initio* molecular dynamics study of ethylene adsorption onto Si(001) surface: Short-time fourier transform analysis of structural coordinate autocorrelation function ,**Yung Ting Lee, Jyh Shing Lin [Tamkang University]

See Applications / Surface, catalysts, and Materials subjects

2707–2715 **Comparison of the capillary wave method and pressure tensor route for calculation of interfacial tension in molecular dynamics simulations ,**Stella Nickerson, Denzil S. Frost,Harrison Phelan, Lenore L. Dai [Arizona State University]

See Applications / Surface, catalysts, and Materials subjects

2716–2725 **Modeling disordered morphologies in organic semiconductors ,**Tobias Neumann, Denis Danilov,Christian Lennartz, Wolfgang Wenzel [Karlsruhe Institute of Technology]

Organic thin film devices are investigated for many diverse applications, including light emitting diodes, organic photovoltaic and organic field effect transistors. . Because time-scales for the formation of the molecular structure are slow, we have developed a linear-scaling single molecule deposition protocol which generates morphologies by simulation of vapor deposition of molecular films.

2726–2741 **Absolute free energies of biomolecules from unperturbed ensembles ,**Gevorg Grigoryan [Dartmouth College]

See Applications / Free Energy Calculations.

2742–2756 **Monte carlo simulations of proteins at constant pH with generalized born solvent, flexible sidechains, and an effective dielectric boundary ,**Savvas Polydorides, Thomas Simonson [Ecole Polytechnique]

See Applications / Protein Dynamics.

Journal of Molecular Modeling, 19 (11), November 2013.

4631-4637 **Computational and experimental studies of the electronic excitation spectra of EDTA and DTPA substituted tetraphenylporphyrins and their Lu complexes ,**Rashid R. Valiev [Tomsk State University], Elena G. Ermolina, Rimma T. Kuznetsova,Victor N. Cherepanov, Dage Sundholm

Ethylendiaminetetraacetic acid (EDTA) substituted and diethylenetriaminopentaacetic acid (DTPA) substituted aminated free-base tetraphenylporphyrins (H_2ATPP) and the corresponding lutetium(III) complexes have been studied computationally at the density functional theory (DFT) and second-order algebraic diagrammatic construction (ADC(2)) levels using triple-ξ basis sets augmented with polarization functions.

4639-4650 **Theoretical study of electronic absorptions in aminopyridines – TCNE CT complexes by quantum chemical methods, including solvent ,**Pavel Mach [Comenius University], György Juhász, Ondrej Kyseľ

The geometric and electronic structure of donor-acceptor complexes of TCNE with aniline, o-, m- and p-aminopyridines and pyridine has been studied in gas phase and in solution using CC2, TDDFT and CIS methods.

4723-4730 **Effect of the aminoacid composition of model α-helical peptides on the physical properties of lipid bilayers and peptide conformation: a molecular dynamics simulation ,**Milan Melicherčík [Comenius University], Alžbeta Holúbeková, Tibor Hianik, Ján Urban

See Applications / Menbrane Protein and Lipid-Peptide interactions.

4731-4740 **The use of supramolecular structures as protein ligands ,**Barbara Stopa, Anna Jagusiak, Leszek Konieczny, Barbara Piekarska, Janina Rybarska, Grzegorz Zemanek, Marcin Król, Piotr Piwowar, Irena Roterman [Jagiellonian University - Medical College]

Congo red dye as well as other eagerly self-assembling organic molecules which form rod-like or ribbon-like supramolecular structures in water solutions, appears to represent a new class of protein ligands with possible wide-ranging medical applications. Such molecules associate with proteins as integral clusters and preferentially penetrate into areas of low molecular stability. Of particular interest is the observation that local susceptibility for binding supramolecular ligands may be promoted in some proteins as a consequence of function-derived structural changes, and that such complexation may alter the activity profile of target proteins. Examples are presented in this paper.

4741-4751 **Theoretical studies on the structure, thermochemical and detonation properties of amino and nitroso substituted 1,2,4-triazol-5-one-N-oxides ,**P. Ravi [University of Hyderabad], V. Venkatesan, Surya P. TewariPages

DFT calculations at the B3LYP/aug-cc-pVDZ level have been carried out to explore the structure, stability, electron density, heat of formation, detonation velocity and detonation pressure of substituted amino- and nitroso-1,2,4-triazol-5-one-N-oxides.

4753-4761 **Stereoselectivity of chalcone isomerase with chalcone derivatives: a computational study ,**Yuan Yao, Hui Zhang, Ze-Sheng Li [Harbin Institute of Technology]

See Applications / Ligand Binding.

4763-4772 **Do coinage metal anions interact with substituted benzene derivatives? ,**Zahra Aliakbar Tehrani, Zahra Jamshidi, Hossein Farhangian

The nature of the anion–π interaction has been investigated by carrying out ab initio calculations of the complexes of coinage metal anions (Au^-, Ag^-, and Cu^-) with different kinds of π-systems.

4773-4780 **Molecular basis of lateral force spectroscopy nano-diagnostics: computational unbinding of autism related chemokine MCP-1 from IgG antibody ,**Anna Gogolinska, Wieslaw Nowak [Nicolaus Copernicus University]

See Methodology / Homology Modeling.

4781-4788 **Influence of doped nitrogen and vacancy defects on the thermal conductivity of graphene nanoribbons ,**Haiying Yang, Yunqing Tang, Jie Gong, Yu Liu, Xiaoliang Wang, Yanfang Zhao, Ping Yang, Shuting Wang [Huazhong University of Science and Technology]

A systematic investigation of the thermal conductivity of zigzag graphene nanoribbons (ZGNRs) doped with nitrogen and containing a vacancy defect was performed using reverse nonequilibrium molecular dynamics

(RNEMD). The investigation showed that the thermal conductivity of the ZGNRs was significantly reduced by nitrogen doping.

4789-4795 **Thiophenic compounds adsorption on Na(I)Y and rare earth exchanged Y zeolites: a density functional theory study ,**Xionghou Gao [Lanzhou Petrochemical Research Center], Wei Geng, Haitao Zhang, Xuefei Zhao, Xiaojun Yao

We have theoretically investigated the adsorption of thiophene, benzothiophene, dibenzothiophene on Na(I)Y and rare earth exchanged La(III)Y, Ce(III)Y, Pr(III)Y Nd(III)Y zeolites by density functional theory calculations.

4797-4804 **Theoretical study on cooperative effects between X···N and X···Carbene halogen bonds (X = F,Cl,Br and I) ,**Mehdi D. Esrafili [University of Maragheh], Fariba Mohammdain-Sabet, Parvin Esmailpour

Quantum chemical calculations are performed to study the interplay between halogen···nitrogen and halogen···carbene interactions in $NCX\cdots NCX\cdots CH_2$ complexes, where X = F, Cl, Br and I. Molecular geometries and interaction energies of dyads and triads are investigated at the MP2/aug-cc-pVTZ level of theory.

4805-4813 **Design of Lewis acid–base complex: enhancing the stability and first hyperpolarizability of large excess electron compound ,**Fang Ma, Tifang Miao, Zhongjun Zhou, Dengming Sun[Huaibei Normal University]

In the present paper, a new type of Lewis acid–base complex BX_3•••Li@Calix[4]pyrrole (X = H and F) was designed and assembled based on electride molecule Li@calix[4]pyrrole (as a Lewis base) and the electron deficient molecule BX_3 (as a Lewis acid) by employing quantum mechanical calculation.

4815-4822 **Theoretical investigation on the kinetics and branching ratio of the gas phase reaction of sevoflurane with Cl atom ,**Hari Ji Singh [DDU Gorakhpur University,], Nand Kishor Gour, Pradeep Kumar Rao, Laxmi Tiwari

The present work deals with the theoretical investigation on the Cl initiated H-atom abstraction reaction of sevoflurane, $(CF_3)_2CHOCH_2F$. A dual-level procedure has been adopted for studying the kinetics of the reaction. Geometrical optimization and frequency calculation were performed at DFT(BHandHLYP)/6-311G(d,p) while single-point energy calculation was made at CCSD(T)/6-311G(d,p) level of theory.

4823-4836 **DFT and docking studies of rhodostreptomycins A and B and their interactions with solvated/nonsolvated Mg^{2+} and Ca^{2+} ions ,**Christiaan Jardínez, Ines Nicolás-Vázquez, Julian Cruz-Borbolla[Unidad Universitaria], Cesar A. González-Ramírez,Miguel Cepeda, Jose Correa-Basurto, Thangarasu Pandiyan, Rene Miranda

See Methodology / Molecular Dynamics.

4837-4847 **Conformational analysis and intramolecular hydrogen bonding of *cis*-3-aminoindan-1-ol: a quantum chemical study ,**Djaffar Kheffache [Université des Sciences et de la Technologie Houari Boumediene USTHB], Hind Guemmour, Azzedine Dekhira, Ahmed Benaboura, Ourida Ouamerali

In the present work, we carried out a conformational analysis of cis-3-aminoindan-1-ol and evaluated the role of the intramolecular hydrogen bond in the stabilization of various conformers using quantum mechanical DFT (B3LYP) and MP2 methods.

4849-4856 **A comparative DFT study on aquation and nucleobase binding of ruthenium (II) and osmium (II) arene complexes ,**Hanlu Wang [Guangdong University of Petrochemical Technology], Xingye Zeng, Rujin Zhou, Cunyuan Zhao

The potential energy surfaces of the reactions of organometallic arene complexes of the type [(η^6-arene)M^{II}(pic)Cl] (where pic = 2-picolinic acid, M = Ru or Os) were examined by a DFT computational study.

4857-4864 **Redox and Lewis acid–base activities through an electronegativity-hardness landscape diagram ,**Ranjita Das, Jean-Louis Vigneresse, Pratim Kumar Chattaraj [Indian Institute of Technology Kharagpur]

Chemistry is the science of bond making and bond breaking which requires redistribution of electron density among the reactant partners. Accordingly acid–base and redox reactions form cardinal components in all branches of chemistry, e.g., inorganic, organic, physical or biochemistry.

4865-4875 **Insight into the structural stability of wild type and mutants of the tobacco etch virus protease with molecular dynamics simulations ,**Yu Wang, Guo-Fei Zhu, Si-Yan Ren, Yong-Guang Han, Yue Luo, Lin-Fang Du [Sichuan University]

See Applications / Protein Structure Analysis.

4877-4886 **Exploring surface reactivity of phosphorous-doped (6,0) and (4,4) BC3 nanotubes: a DFT study** Mohammad Alizadeh, Mehdi D. Esrafili [University of Maragheh], Esmail Vessally

We report a density functional theory study on the electronic structure properties of pristine and phosphorous-doped (6,0) and (4,4) single-walled BC3 nanotubes (BC3NTs). We examine the usefulness of local reactivity descriptors to predict the reactivities of different carbon/boron atomic sites on the external surface of the tubes

4887-4895 **Discovery of σ-hole interactions involving ylides** Jiannan Ji, Yanli Zeng, Xueying Zhang, Shijun Zheng, Lingpeng Meng[Hebei Normal University]

The positive electrostatic potentials (σ-hole) have been found in ylides CH_2XH_3 (X = P, As, Sb) and CH_2YH_2 (Y = S, Se, Te), on the outer surfaces of group VA and VIA atoms, approximately along the extensions of the C–X and C–Y bonds, respectively.

4897-4908 **The intrinsic helical propensities of the helical fragments in prion protein under neutral and low pH conditions: a replica exchange molecular dynamics study** ,Xiaoliang Lu, Juan Zeng, Ya Gao, John Z. H. Zhang, Dawei Zhang, Ye Mei[East China Normal University]

See Applications / Protein Dynamics.

4909-4917 **Easy methods to study the smart energetic TNT/CL-20 co-crystal ,**Huarong Li, Yuanjie Shu [China Academy of Engineering Physic], Shijie Gao, Ling Chen, Qing Ma, Xuehai Ju

2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20) is a high-energy nitramine explosive with high mechanical sensitivity. 2,4,6-trinitrotoluene (TNT) is insensitive but by no means a high performance explosive. To reveal the significant importance and smart-material functionality of the energetic-energetic co-crystals, the stability, mechanical and explosive properties TNT/CL-20 co-crystal, TNT crystal and CL-20 crystal were studied.

4919-4930 **Molecular interactions between fenoterol stereoisomers and derivatives and the β_2-adrenergic receptor binding site studied by docking and molecular dynamics simulations** ,Anita Plazinska, Michal Kolinski, Irving W. Wainer, Krzysztof Jozwiak [Medical University of Lublin]

See Applications / Homology Modeling.

4931-4945 **Conformational flexibility of the leucine binding protein examined by protein domain coarse-grained molecular dynamics ,**Iwona Siuda, Lea Thøgersen [Aarhus University]

See Applications / Protein Confirmational Analysis.

4947-4958 **A DFT study of the Al_2Cl_6-catalyzed Friedel–Crafts acylation of phenyl aromatic compounds** Sigismund T. A. G. Melissen, Vincent Tognetti, Georges Dupas, Julien Jouanneau, Guillaume Lê, Laurent Joubert [Université de Rouen]

The reaction pathways of several Friedel–Crafts acylations involving phenyl aromatic compounds were studied using density functional theory. The reactions were related to the Friedel–Crafts polycondensation of polyaryletherketones. In particular, the acylation of benzene with benzoyl chloride to form benzophenone and variations on this reaction were investigated.

4959-4967 **Effect of surface hydroxyls on dimethyl ether synthesis over the γ-Al_2O_3 in liquid paraffin: a computational study** ,Zhi-jun Zuo, Le Wang, Pei-de Han, Wei Huang [Key Laboratory of Coal Science and Technology of Ministry of Education and Shanxi Province]

In a recent paper (Zuo et al., Appl Catal A 408:130–136, 2011), the mechanism of dimethyl ether (DME) synthesis from methanol dehydration over γ-Al_2O_3 (110) was studied using density functional theory (DFT). Using the same method, the effect of surface hydroxyls on γ-Al_2O_3 in liquid paraffin during DME synthesis from methanol dehydration is investigated.

4969-4989 **Destabilization of the MutSα's protein-protein interface due to binding to the DNA adduct induced by anticancer agent carboplatin via molecular dynamics simulations** ,Lacramioara Negureanu, Freddie R. Salsbury Jr [Wake Forest University]

See Applications / Protein-Protein interaction.

4991-4996 **Armchair BN nanotubes—levothyroxine interactions: a molecular study ,**E. Chigo Anota [Ciudad Universitaria], Gregorio H. Cocoletzi, J. F. Sánchez Ramírez

The density functional theory has been applied to investigate the structural and electronic properties of single-wall boron nitride nanotubes (SW-BNNT) of (5,5) chirality, with surface and ends functionalized by the drug levothyroxine ($C_{15}H_{11}NI_4O_4$).

4997-5006 **The study of interactions between DNA and PcrA DNA helicase by using targeted molecular dynamic simulations ,**Hao Wang [Ningxia Medical University], Jiajia Cui, Wei Hong, Ian C. Paterson, Charles A. Laughton

See Applications / Protein-Nucleic acids.

5007-5014 **The competition of C-X···O=P halogen bond and π-hole ···O=P bond halopentafluorobenzenes C_6F_5X (X=F, Cl, Br, I) and triethylphosphine oxide** ,Xiao Ran Zhao, Hui Wang, Wei Jun Jin [Beijing Normal University]

Calculation predicted the interacting forms of halopentafluorobenzene C_6F_5X (X=F, Cl, Br, I) with triethylphosphine oxide which is biologically interested and easily detected by ^{31}P NMR.

5015-5030 **A knowledge-based halogen bonding scoring function for predicting protein-ligand interactions** Yingtao Liu, Zhijian Xu, Zhuo Yang, Kaixian Chen, Weiliang Zhu [Chinese Academy of Sciences]

See Applications / Menbrane Protein and Lipid-Peptide interactions.

5031-5035 **Competition and interplay between the lithium bonding and hydrogen bonding: $R_3C\cdots HY\cdots LiY$ and $R_3C\cdots LiY\cdots HY$ triads as a working model (R=H, CH_3; Y=CN, NC) ,**Mohammad Solimannejad [Arak University], Zahra Rezaei, Mehdi D. EsrafiliPages

UMP2 calculations with aug-cc-pVDZ basis set were used to analyze intermolecular interactions in $R_3C\cdots HY\cdots LiY$ and $R_3C\cdots LiY\cdots HY$ triads (R=H, CH_3; Y=CN, NC), which are connected via lithium and hydrogen bonds.

5037-5043 **Theoretical investigations on the synthesis mechanism of cyanuric acid from $NH_3$and CO_2 ,**Xueli Cheng [Shandong University], Yanyun Zhao, Weiqun Zhu, Yongjun Liu

In the synthesis of cyanuric acid from NH_3 and CO_2, urea and isocyanic acid OCNH are two pivotal intermediates. Based on density functional theory (DFT) calculations, the synthesis mechanism of cyanuric acid from $NH_3 + CO_2$ was investigated systematically.

5045-5052 **A theoretical investigation on the conformation and the interaction of $CHF_2OCF_2CHF_2$ (desflurane II) with one water molecule ,**Dipankar Sutradhar, Therese Zeegers-Huyskens, Asit K. Chandra [North-Eastern Hill University]

The conformation and the interaction of $CHF_2OCF_2CHF_2$ (desflurane II) with one water molecule is investigated theoretically using the ab initio MP2/aug-cc-pvdz and DFT-based M062X/6-311++G(d,p) methods.

5053-5062 **Molecular dynamics simulation of cross-linked urea-formaldehyde polymers for self-healing nanocomposites: prediction of mechanical properties and glass transition temperature** ,Behrouz Arab [K. N. Toosi University of Technology], Ali Shokuhfar

Urea-formaldehyde polymers, which are utilized in the adhesives industry, have recently been shown to be suitable materials for synthesizing micro/nanocapsules for use in self-healing (nano)composites. In this study, molecular dynamics was employed to simulate the process in which urea and formaldehyde are cross-linked

via methylene and ether cross linkers, and to study the structure and mechanical/thermal properties of simulated poly(urea-formaldehyde)s (PUFs).

5063-5073 **DFT model cluster studies of O2 adsorption on hydrogenated titania sub-nanoparticles ,**Alexey S. Andreev, Vyacheslav N. Kuznetsov [St. Petersburg State University], Yuri V. Chizhov

In the present paper, we examine the general applicability of different TiO_2 model clusters to study of local chemical events on TiO_2 sub-nanoparticles. Our previous DFT study of TiO_2 activation through H adsorption and following deactivation by O_2 adsorption using small amorphous Ti_8O_{16} cluster were complemented by examination of rutile-type and spherical $Ti_{15}O_{30}$ nanoclusters.

5075-5087 **Optimized CGenFF force-field parameters for acylphosphate and N-phosphonosulfonimidoyl functional groups ,**Lamees Hegazy, Nigel G. J. Richards [Indiana University Purdue University Indianapolis]

We report an optimized set of CGenFF parameters that can be used to model small molecules containing acylphosphate and N-phosphonosulfonimidoyl functional groups in combination with the CHARMM force field.

5089-5095 **Gas phase acidities of N-substituted amine-boranes ,**Aiko Adamson [University of Tartu], Jean-Claude Guillemin, Peeter Burk

Complexation energies and acidities of 19 primary, secondary and tertiary amine-boranes were investigated using MP2/6-311+G(d,p) and B3LYP/6-311+G(d,p) methods. Gas phase acidities for free amines were also calculated.

5097-5112 **Binding selectivity studies of PKBα using molecular dynamics simulation and free energy calculations** Shi-Feng Chen, Yang Cao, Jiong-Jiong Chen, Jian-Zhong Chen [Zhejiang University]

See Applications / Medicinal Chemmistry and Drug Design.

5113-5127 **Structure and spectral characteristics of diquat-cucurbituril complexes from density functional theory ,**Swarada R. Peerannawar, Shridhar P. Gejji [University of Pune]

Electronic structure, ^{1}H NMR and infrared spectra of diquat (6,7-dihydrodipyrido[1,2-b:1′,2′-e] pyrazine-5,8-diium or DQ^{2+}) encapsulated by cucurbit[n]uril (n = 7,8) hosts are obtained using the density functional theory.

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