



Results

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1 APPLICATIONS (59) Page 2

1.1 Small Molecules (11)

Med. Chem. And Drug Design	Page 2	Zeolites	Page 5
QSAR	Page 5		

1.2 Biopolymers (48)

Bioinformatics and Cheminformatics	Page 5	Enzyme Catalysis	Page 11
Comparative or Homology Modeling	Page 6	Protein-Protein Interactions	Page 12
Protein Side Chain Confirmation Prediction	Page 7	Membrane Proteins	Page 14
Protein Conformational Analysis	Page 8	Protein Folding	Page 16
Protein Dynamics	Page 8	Protein-Nucleic Acids	Page 17
Free Energy Calculations	Page 9	Nucleic Acids	Page 18
Ligand Binding	Page 10		

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (23) Page 20

Potentials and Parameters	Page 20	QM & QM/MM	Page 23
Molecular Dynamics	Page 20	Comparative or Homology	Page 24
Monte Carlo	Page 22	Ligand Docking	Page 25

3 JOURNAL REVIEWS (3) Page 27

Journal of Computational Chemistry, 33 (2), January, 2012.
 Journal of Computational Chemistry, 33 (3), January, 2012.
 Journal of Molecular Modeling, 17 (12), December, 2011.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 35

5 COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Lose Weight with Traditional Chinese Medicine? Potential Suppression of Fat Mass and Obesity-Associated Protein

Pei-Chun Changa#, Jing-Doo Wanga#, Min-Min Leea#, Su-Sen Chang, Tsung-Ying Tsai, Kai-Wei Chang, Fuu-Jen Tsai, Calvin Yu-Chian Chen [Asia University]

J. Biomol. Stru. and Dyn., **29**, 471-483, 2011.

Overweight and obesity are common health problems in modern society, particularly in developed countries. Excessive body mass has been linked to numerous diseases, such as cardiovascular diseases, diabetes, and cancer. Fat mass and obesity-associated protein (FTO) activity have direct impact on food intake and results in obesity. Inhibition of FTO activity may cause weight loss and reduce obese-linked health risks. We investigated the potential weight loss effects of traditional Chinese medicine (TCM), particularly by inhibiting FTO functions. Molecular docking was performed to screen TCM compounds from TCM Database@Taiwan.

Effects of nanoparticles on the compatibility of PEO-PMMA block copolymers

Dan Mu [Zaozhuang University], Jian-Quan Li, Wei-Dong Li and Song Wang

J. Mol.Mod., **17**, 3027-3038, 2011.

Snake venom, particularly of vipers from the Indian subcontinent, contains Phospholipase A2 (PLA2) as one its constituents which is widely implicated in hemorrhagic, cardiac arrest and death. Development of inhibitors of the protein can facilitate the weakening or annihilation of the venom toxicity and save many human lives. In the present communication, our studies relate to the design and development of structure-based ligands as inhibitors of PLA2 of Viper venom. The study involves the computational approach towards evaluating a library of molecules comprising of natural products, and synthetic molecules through docking studies on the venom protein PDB ID: 1OXL (a dimer, available in the literature).



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Medicinal Chemistry and Drug Design (Cont'd)

Integrative computational protocol for the discovery of inhibitors of the *Helicobacter pylori* nickel response regulator (NikR)

Aldo Segura-Cabrera [Boulevard del Maestro esquina Elías Piña], Xianwu Guo, Arturo Rojo-Domínguez and Mario A. Rodríguez-Pérez

J. Mol. Mod., **17**, 3075-3084, 2011.

In order to identify novel inhibitors of the *Helicobacter pylori* nickel response regulator (HpNikR) an integrative protocol was performed for half a million compounds retrieved from the ZINC database. We firstly implement a structure-based virtual screening to build a library of potential inhibitors against the HpNikR using a docking analysis (AutoDock Vina). The library was then used to perform a hierarchical clustering of docking poses, based on protein-contact footprints calculation from the multiple conformations given by the AutoDock Vina software, and the drug-protein interaction analyses to identify and remove potential promiscuous compounds likely interacting with human proteins, hence causing drug side effects.

Investigation of the Differences in Activity between Hydroxycycloalkyl N1 Substituted Pyrazole Derivatives As Inhibitors of B-Raf Kinase by Using Docking, Molecular Dynamics, QM/MM, and Fragment-Based De Novo Design: Study of Binding Mode of Diastereomer Compounds

Julio Caballero [Universidad de Talca], Jans H. Alzate-Morales, and Ariela Vergara-Jaque

J. Chem. Infor. and Mod. **51**, 2920–2931, 2011.

N1 substituted pyrazole derivatives show diverse B-Raf kinase inhibitory activities when different hydroxy-substituted cycloalkyl groups are placed at this position. Docking, molecular dynamics (MD) simulations, and hybrid calculation methods (Quantum Mechanics/Molecular Mechanics (QM/MM)) were performed on the complexes, in order to explain these differences. Docking of the inhibitors showed the same orientation that X-ray crystal structure of the analogous (1E)-5-[1-(4-piperidiny)-3-(4-pyridiny)-1H-pyrazol-4-yl]-2,3-dihydro-1H-inden-1-one oxime. We also explained the activity trend by using a testing scoring function derived from more reliable QM/MM calculations.

IDSite: An Accurate Approach to Predict P450-Mediated Drug Metabolism

Jianing Li, Severin T. Schneebeli, Joseph Bylund, Ramy Farid, and Richard A. Friesner [Columbia University]

J. Chem. Theor. and Comp., **7**, 3829–3845, 2011.

Accurate prediction of drug metabolism is crucial for drug design. Since a large majority of drugs' metabolism involves P450 enzymes, we herein describe a computational approach, IDSite, to predict P450-mediated drug metabolism. To model induced-fit effects, IDSite samples the conformational space with flexible docking in Glide followed by two refinement stages using the Protein Local Optimization Program (PLOP). Sites of metabolism (SOMs) are predicted according to a physical-based score that evaluates the potential of atoms to react with the catalytic iron center.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of Novel Inhibitors of Tropomyosin-Related Kinase A through the Structure-Based Virtual Screening with Homology-Modeled Protein Structure

Hwangseo Park [Sejong University], Okyung Chi, Jinhee Kim, and Sungwoo Hong

J.Chem. Infor. and Mod. **51**, 2986–2993, 2011.

Tropomyosin-related kinase A (TrkA) is a promising target for the development of cancer and pain therapeutics. Here, we report the first successful example of the use of a structure-based virtual screening to identify novel TrkA inhibitors. The accuracy of the virtual screening was improved by introducing an accurate solvation free energy term into the original AutoDock scoring function. We applied a drug design protocol involving homology modeling, docking analysis of a large chemical library, and enzyme inhibition assays to identify six structurally diverse TrkA inhibitors with K_d values ranging from 3 to 40 μ M.

Novel 1-Hydroxypiperazine-2,6-diones as New Leads in the Inhibition of Metalloproteinases

Sérgio M. Marques, Tiziano Tuccinardi, Elisa Nuti, Salvatore Santamaria, Vânia André, Armando Rossello, Adriano Martinelli, and M. Amélia Santos [Instituto Superior Técnico]

J.Med.Chem. **54**, 7663–7677, 2011.

New compounds containing a novel zinc-binding group (1-hydroxypiperazine-2,6-dione, HPD) have been identified as effective inhibitors of matrix metalloproteinases (MMPs), with activities in the nanomolar concentration range. That moiety seemed to bind the catalytic zinc ion of MMPs, revealing itself as a new potential substitute for the hydroxamate group in the next generation of metalloproteinase inhibitors. A computational method involving docking and hybrid quantum mechanical and molecular mechanical (QM/MM) dynamic simulations was developed and applied.

Synthesis and Biological Characterization of 3-Substituted-1H-indoles as Ligands of GluN2B-Containing N-Methyl-D-aspartate Receptors

Rosaria Gitto [Università di Messina], Laura De Luca, Stefania Ferro, Maria Rosa Buemi, Emilio Russo, Giovambattista De Sarro, Lara Costa, Lucia Ciranna, Orazio Prezzavento, Emanuela Arena, Simone Ronsisvalle, Giuseppe Bruno, and Alba Chimirri

J.Med.Chem. **54**, 8702–8706, 2011.

As an extension of our studies, novel indole derivatives were rationally designed and synthesized as ligands targeted to GluN2B/NMDA receptors. The 2-(4-benzylpiperidin-1-yl)-1-(6-hydroxy-1H-indol-3-yl)ethanone (**4i**) and 1-(4-benzylpiperidin-1-yl)-2-(6-hydroxy-1H-indol-3-yl)ethane-1,2-dione (**6i**) showed high binding affinity in [^{3} H]ifenprodil displacement assay. By computational studies, we suggested the hypothetical interactions playing a significant role during the binding process. However, in functional and in vivo studies the most potent compound **4i** did not show any activity whereas it displayed relevant affinity toward the σ_2 receptor.

Molecular Dynamics Simulations of the Effect of the G-Protein and Diffusible Ligands on the β_2 -Adrenergic Receptor

Angela Goetz, Harald Lanig, Peter Gmeiner, Timothy Clark [University of Portsmouth]

J. Molec. Bio. **414**, 16-26, 2011.

G-protein-coupled receptors have extraordinary therapeutic potential as targets for a broad spectrum of diseases. Understanding their function at the molecular level is therefore essential. A variety of crystal structures have made the investigation of the inactive receptor state possible. Recently released X-ray structures of opsin and the β_2 -adrenergic receptor (β_2 AR) have provided insight into the active receptor state. In addition, we have contributed to the crystal structure of an irreversible agonist- β_2 adrenoceptor complex.

Quantitative Structure-Activity Relations

A combined molecular modeling study on a series of pyrazole/isoxazole based human Hsp90 α inhibitors

Ying Yang, Huanxiang Liu, Juan Du, Jin Qin and Xiaojun Yao [Lanzhou University]

J. Mol.Mod., **17**, 3241-3250, 2011.

Inhibition of the protein chaperone Hsp90 α is a promising approach for cancer therapy. In this work, a molecular modeling study combining pharmacophore model, molecular docking and three-dimensional quantitative structure-activity relationships (3D-QSAR) was performed to investigate a series of pyrazole/isoxazole scaffold inhibitors of human Hsp90 α . The pharmacophore model can provide the essential features required for the biological activities of the inhibitors. The molecular docking study can give insight into the binding mode between Hsp90 α and its inhibitors.

Zeolites

Understanding the Equilibrium Ion Exchange Properties in Faujasite Zeolite from Monte Carlo Simulations

Marie Jeffroy, Anne Boutin, and Alain H. Fuchs [CNRS-ENS-UPMC]

J. Phys. Chem. B., **115**, 15059–15066, 2011.

We have adapted a grand ensemble Monte Carlo simulation method to directly compute, for the first time to our knowledge, univalent cation exchange isotherms in zeolites. The computed isotherms for the exchange of sodium in NaY faujasite by lithium, potassium, rubidium, and cesium ions, respectively, are in good agreement with the experimental ones. They display the three main types of behavior observed in zeolites, namely, a monotonous evolution of selectivity throughout the exchange process (Li^+), a selectivity reversal (K^+), and an incomplete exchange (Rb^+ and Cs^+).

1.2. Biopolymers

Bioinformatics and Cheminformatics

NNScore 2.0: A Neural-Network Receptor–Ligand Scoring Function

Jacob D. Durrant [University of California San Diego] and J. Andrew McCammon

J.Chem. Infor. and Mod. **51**, 2897–2903, 2011.

NNScore is a neural-network-based scoring function designed to aid the computational identification of small-molecule ligands. While the test cases included in the original NNScore article demonstrated the utility of the program, the application examples were limited. The purpose of the current work is to further confirm that neural-network scoring functions are effective, even when compared to the scoring functions of state-of-the-art docking programs, such as AutoDock, the most commonly cited program, and AutoDock Vina, thought to be two orders of magnitude faster.

Bioinformatics and Cheminformatics (Cont'd)

Micellization Studied by GPU-Accelerated Coarse-Grained Molecular Dynamics

Benjamin G. Levine, David N. LeBard, Russell DeVane, Wataru Shinoda, Axel Kohlmeyer, and Michael L. Klein [Temple University, Philadelphia]

J. Chem. Theor. and Comp., **7**, 4135–4145, 2011.

The computational design of advanced materials based on surfactant self-assembly without ever stepping foot in the laboratory is an important goal, but there are significant barriers to this approach, because of the limited spatial and temporal scales accessible by computer simulations. In this paper, we report our work to bridge the gap between laboratory and computational time scales by implementing the coarse-grained (CG) force field previously reported by Shinoda et al. into the HOOMD-Blue graphical processing unit (GPU)-accelerated molecular dynamics (MD) software package previously reported by Anderson et al.

Comparative or Homology Modeling

Homology modeling and in silico screening of inhibitors for the substrate binding domain of human Siah2: implications for hypoxia-induced cancers

Gopalsamy Anupriya, Kothapalli Roopa, S. Basappa, Yap Seng Chong and Loganath Annamalai [National University of Singapore]

J. Mol. Mod., **17**, 3325–3332, 2011.

The three-dimensional (3D) structure of the substrate binding domain (SBD) of human ubiquitin ligase Siah2 (seven in absentia homolog) was constructed based on the homology modeling approach using the Modeller 9v7 program. The molecular dynamics method was utilized to refine the model and it was further assessed by ProSA, three-dimensional structural superposition (3d-SS) and PROCHECK in order to analyze the quality and reliability of the generated model. Furthermore, we predicted the binding pocket of Siah2 and also validated it by both blind and normal docking using a known functional inhibitor, menadione.

Molecular Modeling of Neurokinin B and Tachykinin NK₃ Receptor Complex

Anjali D. Ganjiwale, Gita Subba Rao, and Sudha M. Cowsik [Jawaharlal Nehru University]

J. Chem. Infor. and Mod. **51**, 2932–2938, 2011.

The tachykinin receptor NK₃ is a member of the rhodopsin family of G-protein coupled receptors. The NK₃ receptor has been regarded as an important drug target due to diverse physiological functions and its possible role in the pathophysiology of psychiatric disorders, including schizophrenia. Agonist binding to the receptor is a critical event in initiating signaling, and therefore a characterization of the structural features of the agonists can reveal the molecular basis of receptor activation and help in rational design of novel therapeutics. In this study a molecular model for the interaction of the primary ligand NKB with its G-protein coupled receptor NK₃ has been developed.

Comparative or Homology Modeling (Cont'd)

Identification of Inhibitors against p90 Ribosomal S6 Kinase 2 (RSK2) through Structure-Based Virtual Screening with the Inhibitor-Constrained Refined Homology Model

Shiliang Li, Yi Zhou, Weiqiang Lu, Ye Zhong, Wenlong Song, Kangdong Liu, Jin Huang, Zhenjiang Zhao, Yufang Xu, Xiaofeng Liu [East China University of Science and Technology], and Honglin Li

J.Chem. Infor. and Mod. **51**, 2939–2947, 2011.

P90 ribosomal S6 kinase 2 (RSK2), which was shown to be overexpressed in human cancers, is a serine/threonine kinase and a potential target for cancer treatment. RSK2 comprises two terminal kinase domains (NTKD and CTKD) that can be inhibited by binding with different types of inhibitors at the ATP binding sites. In the absence of a crystal structure of RSK2, we constructed a model for the 3D structure of the RSK2 NTKD by homology modeling and stepwise constrained refinement with the reported inhibitors using a molecular docking method.

A Critical Assessment of Combined Ligand- and Structure-Based Approaches to hERG Channel Blocker Modeling

Lei Du-Cuny, Lu Chen, and Shuxing Zhang [The University of Texas]

J.Chem. Infor. and Mod. **51**, 2948–2960, 2011.

Blockade of human ether-à-go-go related gene (hERG) channel prolongs the duration of the cardiac action potential and is a common reason for drug failure in preclinical safety trials. Therefore, it is of great importance to develop robust in silico tools to predict potential hERG blockers in the early stages of drug discovery and development. Herein we described comprehensive approaches to assess the discrimination of hERG-active and -inactive compounds by combining quantitative structure–activity relationship (QSAR) modeling, pharmacophore analysis, and molecular docking.

Protein Side-Chain Confirmation Prediction

SIDEpro: A novel machine learning approach for the fast and accurate prediction of side-chain conformations

Ken Nagata, Arlo Randall and Pierre Baldi [University of California]

Proteins: Stru. Fun. & Bioinf. **80**, 142–153, 2012.

Accurate protein side-chain conformation prediction is crucial for protein modeling and existing methods for the task are widely used; however, faster and more accurate methods are still required. Here we present a new machine learning approach to the problem where an energy function for each rotamer in a structure is computed additively over pairs of contacting atoms. A family of 156 neural networks indexed by amino acid and contacting atom types is used to compute these rotamer energies as a function of atomic contact distances.

Protein Conformational Analysis

Explaining the Structural Plasticity of α -Synuclein

Orly Ullman, Charles K. Fisher, and Collin M. Stultz
[Massachusetts Institute of Technology]

J. Am. Chem. Soc., **133**, 19536–19546, 2011.

Given that α -synuclein has been implicated in the pathogenesis of several neurodegenerative disorders, deciphering the structure of this protein is of particular importance. While monomeric α -synuclein is disordered in solution, it can form aggregates rich in cross- β structure, relatively long helical segments when bound to micelles or lipid vesicles, and a relatively ordered helical tetramer within the native cell environment. To understand the physical basis underlying this structural plasticity, we generated an ensemble for monomeric α -synuclein using a Bayesian formalism that combines data from NMR chemical shifts, RDCs, and SAXS with molecular simulations.

Determination of Conformational Equilibria in Proteins Using Residual Dipolar Couplings

Alfonso De Simone, Rinaldo W. Montalvao, and Michele Vendruscolo [University of Cambridge]

J. Chem. Theor. and Comp., **7**, 4189–4195, 2011.

In order to carry out their functions, proteins often undergo significant conformational fluctuations that enable them to interact with their partners. The accurate characterization of these motions is key in order to understand the mechanisms by which macromolecular recognition events take place. Nuclear magnetic resonance spectroscopy offers a variety of powerful methods to achieve this result. We discuss a method of using residual dipolar couplings as replica-averaged restraints in molecular dynamics simulations to determine large amplitude motions of proteins, including those involved in the conformational equilibria that are established through interconversions between different states.

Protein Dynamics

Molecular Simulation Uncovers the Conformational Space of the λ Cro Dimer in Solution

Logan S. Ahlstrom, Osamu Miyashita [University of Arizona]

Biophysical Journal. **101**, 2516–2524, 2011.

The significant variation among solved structures of the λ Cro dimer suggests its flexibility. However, contacts in the crystal lattice could have stabilized a conformation which is unrepresentative of its dominant solution form. Here we report on the conformational space of the Cro dimer in solution using replica exchange molecular dynamics in explicit solvent. The simulated ensemble shows remarkable correlation with available x-ray structures. Network analysis and a free energy surface reveal the predominance of closed and semi-open dimers, with a modest barrier separating these two states.

Protein Dynamics (Cont'd)

Rapid Assembly of a Multimeric Membrane Protein Pore

James R. Thompson, Bríd Cronin, Hagan Bayley, Mark I. Wallace [University of Oxford]

Biophysical Journal. **101**, 2679-2683, 2011.

We have observed the assembly of the staphylococcal pore-forming toxin α -hemolysin using single-molecule fluorescence imaging. Surprisingly, assembly from the monomer to the complete heptamer is extremely rapid, occurring in <5 ms. No lower order oligomeric intermediates are detected. Monte Carlo simulation of our experiment shows that assembly is diffusion limited, and pore formation is dependent on the stability of intermediate species. The assembly mechanism we have observed for α -hemolysin provides a simple model that aids our understanding of these important pore formers.

Crowding Induces Differences in the Diffusion of Thermophilic and Mesophilic Proteins: A New Look at Neutron Scattering Results

Enrique Marcos, Pau Mestres, Ramon Crehuet [IQAC – CSIC]

Biophysical Journal. **101**, 2782-2789, 2011.

The dynamical basis underlying the increased thermal stability of thermophilic proteins remains uncertain. Here, we challenge the new paradigm established by neutron scattering experiments in solution, in which the adaptation of thermophilic proteins to high temperatures lies in the lower sensitivity of their flexibility to temperature changes. By means of a combination of molecular dynamics and Brownian dynamics simulations, we report a reinterpretation of those experiments and show evidence that under crowding conditions, such as in vivo, thermophilic and homolog mesophilic proteins have diffusional properties with different thermal behavior.

A GRID-Derived Water Network Stabilizes Molecular Dynamics Computer Simulations of a Protease

Hannes G. Wallnoefer, Klaus R. Liedl [University of Innsbruck], and Thomas Fox

J.Chem. Infor. and Mod. **51**, 2860–2867, 2011.

Structural water molecules are crucial for the stability and function of proteins. Recently, we presented a molecular dynamics (MD) study on blood coagulation factor Xa (fXa) to investigate the effect of water molecules on the flexibility of the protein structure. We showed that neglecting important water positions at the outset of the simulation leads to severe structural distortions during the MD simulations: A stable trajectory was obtained with a water set that was derived from all 73 X-ray structures of the protein.

Free Energy Calculations

The linear interaction energy method for the prediction of protein stability changes upon mutation

Lauren Wickstrom, Emilio Gallicchio and Ronald M. Levy [The State University of New Jersey]

Proteins: Stru. Fun. & Bioinf. **80**, 111–125, 2012.

The coupling of protein energetics and sequence changes is a critical aspect of computational protein design, as well as for the understanding of protein evolution, human disease, and drug resistance. To study the molecular basis for this coupling, computational tools must be sufficiently accurate and computationally inexpensive enough to handle large amounts of sequence data. We have developed a computational approach based on the linear interaction energy (LIE) approximation to predict the changes in the free-energy of the native state induced by a single mutation.

Ligand Binding/Docking

Computational Study of the Binding Modes of Caffeine to the Adenosine A_{2A} Receptor

Yuli Liu, Steven K. Burger, and Paul W. Ayers [McMaster University], Esteban Vöhringer-Martinez

J. Phys. Chem. B., **115**, 13880–13890, 2011.

Using the recently solved crystal structure of the human adenosine A_{2A} receptor, we applied MM/PBSA to compare the binding modes of caffeine with those of the high-affinity selective antagonist ZM241385. MD simulations were performed in the environment of the lipid membrane bilayer. Four low-energy binding modes of caffeine-A_{2A} were found, all of which had similar energies. Assuming an equal contribution of each binding mode of caffeine, the computed binding free energy difference between caffeine and ZM241385 is −2.4 kcal/mol, which compares favorably with the experimental value, −3.6 kcal/mol.

Modeling the Binding of Three Toxins to the Voltage-Gated Potassium Channel (Kv1.3)

Rong Chen, Anna Robinson, Dan Gordon, Shin-Ho Chung [Australian National University, Canberra]

Biophysical Journal. **101**, 2652-2660, 2011.

The conduction properties of the voltage-gated potassium channel Kv1.3 and its modes of interaction with several polypeptide venoms are examined using Brownian dynamics simulations and MD calculations. Employing an open-state homology model of Kv1.3, we first determine current-voltage and current-concentration curves and ascertain that simulated results accord with experimental measurements. We then investigate, using a molecular docking method and MD simulations, the complexes formed between the Kv1.3 channel and several Kv-specific polypeptide toxins that are known to interfere with the conducting mechanisms of several classes of voltage-gated K⁺ channels.

Permeation and Block of the Kv1.2 Channel Examined Using Brownian and Molecular Dynamics

Dan Gordon, [Australian National University, Canberra], Shin-Ho Chung

Biophysical Journal. **101**, 2671-2678, 2011.

Using both Brownian and molecular dynamics, we replicate many of the salient features of Kv1.2, including the current-voltage-concentration profiles and the binding affinity and binding mechanisms of charybdotoxin, a scorpion venom. We also elucidate how structural differences in the inner vestibule can give rise to significant differences in its permeation characteristics. Current-voltage-concentration profiles are constructed using Brownian dynamics simulations, based on the crystal structure 2A79. The results are compatible with experimental data, showing similar conductance, rectification, and saturation with current.

The Effect of Environment on the Recognition and Binding of Vancomycin to Native and Resistant Forms of Lipid II

ZhiGuang Jia, Megan L. O'Mara, Johannes Zuegg, Matthew A. Cooper, Alan E. Mark [The University of Queensland]

Biophysical Journal. **101**, 2684-2692, 2011.

MD simulations and free energy calculations are used to examine the mechanism by which a receptor molecule (the glycopeptide antibiotic vancomycin) recognizes and binds to a target molecule (lipid II) embedded within a membrane environment. The simulations show that the direct interaction of vancomycin with lipid II, as opposed to initial binding to the membrane, leads most readily to the formation of a stable complex. The recognition of lipid II by vancomycin occurred via the N-terminal amine group of vancomycin and the C-terminal carboxyl group of lipid II.

Ligand Binding / Docking (Cont'd)

Molecular dynamics simulation of the *Staphylococcus aureus* YsxC protein: molecular insights into ribosome assembly and allosteric inhibition of the protein

Amit Goyal, Kannan Muthu, Manivel Panneerselvam, Anil Kumar Pole and Krishna Ramadas [Pondicherry University]

J. Mol.Mod., **17**, 3129-3149, 2011.

YsxC from *Staphylococcus aureus* is a member of the GTPase protein family, and is involved in the ribosomal assembly and stability of this microorganism through its interactions with the L17, S2 and S10 ribosomal proteins. Inhibition of its interactions with L17, S2, S10 and the β' subunit of RNA polymerase influences ribosomal assembly, which may affect the growth of the microorganism. This makes YsxC a novel target for the design of inhibitors to treat the disease caused by *S. aureus*. In the present study, an in silico analysis of the interactions between YsxC and L17, S2 and S10 was performed, and the potential residues involved in these interactions were identified.

Enzyme Catalysis

The Effect of Thiobarbituric Acid on Tyrosinase: Inhibition Kinetics and Computational Simulation

Shang-Jun Yin, Yue-Xiu Si, Zhi-Jiang Wang, Su-Fang Wang, Sangho Oh, Sanghyuk Lee, Seon-Mi Sim, Jun-Mo Yang, Guo-Ying Qian, Jinhyuk Lee, Yong-Doo Park [Zhejiang Wanli University]

J. Biomol. Stru. and Dyn., **29**, 463-470, 2011.

Tyrosinase plays various roles in organisms and much research has focused on the regulation of tyrosinase activity. We studied the inhibitory effect of thiobarbituric acid (TBA) on tyrosinase. Our kinetic study showed that TBA inhibited tyrosinase in a reversible noncompetitive manner ($K_i = 14.0 \pm 8.5 \mu\text{M}$ and $IC_{50} = 8.0 \pm 1.0 \mu\text{M}$). Intrinsic and ANS-binding fluorescence studies were also performed to gain more information regarding the binding mechanism. The results showed that no tertiary structural changes were obviously observed. For further insight, we predicted the 3D structure of tyrosinase and simulated the docking between tyrosinase and TBA.

Long range molecular dynamics study of regulation of eukaryotic glucosamine-6-phosphate synthase activity by UDP-GlcNAc

Aleksandra Miszkiewicz, Marek Wojciechowski [Gdansk University of Technology] and Sławomir Milewski

J. Mol.Mod., **17**, 3103-3115, 2011.

Glucosamine-6-phosphate (GlcN-6-P) synthase catalyses the first and practically irreversible step in hexosamine metabolism. The final product of this pathway, uridine 5' diphospho N-acetyl-D-glucosamine (UDP-GlcNAc), is an essential substrate for assembly of bacterial and fungal cell walls. The crystal structure of the isomerase domain of GlcN-6-P synthase from human pathogenic fungus *Candida albicans*, in complex with UDP-GlcNAc has been solved recently but it has not revealed the molecular mechanism of inhibition taking place under UDP-GlcNAc influence, the unique feature of the eukaryotic enzyme. In the present work, comparative molecular dynamics simulations of the free and UDP-GlcNAc-bound structures of GlcN-6-P synthase have been performed.

Enzyme Catalysis (Cont'd)

QM/MM Study of the Catalytic Mechanism of GalNAc Removal from GM2 Ganglioside Catalyzed by Human β -HexosaminidaseA

Óscar Passos, Pedro Alexandrino Fernandes, and Maria João Ramos [Porto University]

J. Phys. Chem. B., **115**, 14751–14759, 2011.

This work is based on the glycosidase β -hexosaminidase, in particular, on β -HexA (HexA), involved in the emergence of the Sandoff disease. Its function is to cleave the N-acetylgalactosamine (GalNAc) or N-acetylglucosamine moieties from its substrates. Here we reveal and consolidate many important aspects of the catalytic mechanism of GalNAc removal from the GM2 ganglioside. The reaction mechanism for this reaction is proposed to be substrate-assisted. It is expected to evolve through a mechanism similar to others glycosidase mechanisms, even though this fact has never been confirmed and the proposal still lacks atomic level detail in its description.

Allosteric regulation of PKC θ : Understanding multistep phosphorylation and priming by ligands in AGC kinases

Jesus Seco, Carles Ferrer-Costa, Josep M. Campanera, Robert Soliva [Facultat de Farmàcia, Av. Joan XXIII s/n] and Xavier Barril

Proteins: Stru. Fun. & Bioinf. **80**, 269–280, 2012.

Protein kinases play critical roles in cellular activation and differentiation, and are involved in numerous pathophysiological processes. As a critical component of the regulatory circuitry of the cell, the kinase domain has the ability to integrate multiple signals, yielding a predetermined output. In PKC and other protein kinases of the AGC family, several phosphorylation sites control the activity, but these are in turn influenced by the presence of ligands in the binding pocket, which promotes phosphorylation. Here, we take PKC- θ as a prototypical member of the family and use molecular dynamics simulations to investigate the cross-talk that exists between regulatory and functional sites.

Protein-Protein Interactions

Thermodynamic Properties of Water Molecules at a Protein–Protein Interaction Surface

David J. Huggins [University of Cambridge], May Marsh, and Mike C. Payne

J. Chem. Theor. and Comp., **7**, 3514–3522, 2011.

Protein–protein interactions (PPIs) have been identified as a vital regulator of cellular pathways and networks. However, the determinants that control binding affinity and specificity at protein surfaces are incompletely characterized and thus unable to be exploited for the purpose of developing PPI inhibitors to control cellular pathways in disease states. In this work, we have studied the protein surface of a mutant of the protein RadA to quantify the thermodynamics of surface water molecules. RadA and its human homologue RAD51 function as recombinases in the process of homologous recombination.

Protein-Protein Interactions (Cont'd)

A novel method for protein–protein interaction site prediction using phylogenetic substitution models

David La and Daisuke Kihara [Purdue University]

Proteins: Stru. Fun. & Bioinf. **80**, 126–141, 2012.

Protein–protein binding events mediate many critical biological functions in the cell. Typically, functionally important sites in proteins can be well identified by considering sequence conservation. Here, we present a phylogenetic framework to capture critical sequence variations that favor the selection of residues essential for protein–protein binding. Through the comprehensive analysis of diverse protein families, we show that protein binding interfaces exhibit distinct amino acid substitution as compared with other surface residues.

Prescont: Predicting protein-protein interfaces utilizing four residue properties

Hermann Zellner, Martin Staudigel, Thomas Trenner, Meik Bittkowski, Vincent Wolowski, Christian Icking and Rainer Merkl [University of Regensburg]

Proteins: Stru. Fun. & Bioinf. **80**, 154–168, 2012.

An important task of computational biology is to identify those parts of a polypeptide chain, which are involved in interactions with other proteins. For this purpose, we have developed the program PresCont, which predicts in a robust manner amino acids that constitute protein–protein interfaces (PPIs). PresCont reaches state-of-the-art classification quality on the basis of only four residue properties that can be readily deduced from the 3D structure of an individual protein and a multiple sequence alignment (MSA) composed of homologs.

On the use of distance constraints in protein–protein docking computations

Edward S. C. Shih and Ming-Jing Hwang [Academia Rd. Nankang]

Proteins: Stru. Fun. & Bioinf. **80**, 194–205, 2012.

Protein–protein docking (PPD) is a computational process that predicts the structure of a complex of two interacting proteins from their unbound structures. The accuracy of PPD predictions is low, but can be greatly enhanced if experimentally determined distance data are available for incorporation into the prediction. However, the specific effects of distance constraints on PPD predictions are largely uncharacterized. In this study, we systematically simulated the effects of using distance constraints both on a new distance constraint-driven PPD approach, called DPPD, and also, by re-ranking, on a well-established grid-based global search approach.

Surface-histogram: A new shape descriptor for protein–protein docking

Shengyin Gu [University of California], Patrice Koehl, Joel Hass and Nina Amenta

Proteins: Stru. Fun. & Bioinf. **80**, 221–238, 2012.

Determining the structure of protein–protein complexes remains a difficult and lengthy process, either by NMR or by X-ray crystallography. Several computational methods based on docking have been developed to support and even serve as possible alternatives to these experimental methods. In this article, we introduce a new protein–protein docking algorithm, shDock, based on shape complementarity. We characterize the local geometry on each protein surface with a new shape descriptor, the surface-histogram.

Membrane Proteins and Lipid Peptide Interactions

Molecular dynamics simulation of hydrated DPPC monolayers using charge equilibration force fields

Timothy R. Lucas, Brad A. Bauer, Joseph E. Davis and Sandeep Patel [University of Delaware]

J. Comp. Chem. **33**, 141–152, 2012.

We present results of MD simulations of a model DPPC-water monolayer using charge equilibration (CHEQ) force fields, which explicitly account for electronic polarization in a classical treatment of intermolecular interactions. The surface pressure, determined as the difference between the monolayer and pure water surface tensions at 323 K, is predicted to be 22.92 ± 1.29 dyne/cm, just slightly below the broad range of experimental values reported for this system. The surface tension for the DPPC-water monolayer is predicted to be 42.35 ± 1.16 dyne/cm, in close agreement with the experimentally determined value of 40.9 dyne/cm.

Analysis of lipid surface area in protein–membrane systems combining voronoi tessellation and monte carlo integration methods

Takaharu Mori, Fumiko Ogushi and Yuji Sugita [RIKEN Quantitative Biology Center]

J. Comp. Chem. **33**, 286–293, 2012.

All-atom MD simulation has become a powerful research tool to investigate structural and dynamical properties of biological membranes and membrane proteins. The lipid structures of simple membrane systems in recent MD simulations are in good agreement with those obtained by experiments. However, for protein–membrane systems, the complexity of protein–lipid interactions makes investigation of lipid structure difficult. To overcome this limitation, we propose a new method combining the two-dimensional Voronoi tessellation and Monte Carlo integration methods.

QM/MM refinement and analysis of protein bound retinoic acid

Xue Li, Zheng Fu and Kenneth M. Merz Jr. [University of Florida]

J. Comp. Chem. **33**, 301–310, 2012.

Retinoic acid (RA) is a vitamin A derivative, which modifies the appearance of fine wrinkles and roughness of facial skin and treats acne and activates gene transcription by binding to heterodimers of the retinoic acid receptor (RAR) and the retinoic X receptor (RXR). There are series of protein bound RA complexes available in the protein databank (PDB), which provides a broad range of information about the different bioactive conformations of RA. To gain further insights into the observed bioactive RA conformations we applied quantum mechanic (QM)/molecular mechanic (MM) approaches to re-refine the available RA protein-ligand complexes.

Statistical Convergence of Equilibrium Properties in Simulations of Molecular Solutes Embedded in Lipid Bilayers

Chris Neale, W. F. Drew Bennett, D. Peter Tieleman, and Régis Pomès [555 University Avenue, Toronto]

J. Chem. Theor. and Comp. **7**, 4175–4188, 2011.

In recent years, atomistic molecular simulations have become a method of choice for studying the interaction of small molecules, peptides, and proteins with biological membranes. Here, we critically examine the statistical convergence of equilibrium properties in molecular simulations of two amino acid side-chain analogs, leucine and arginine, in the presence of a hydrated phospholipid bilayer. To this end, the convergence of the standard binding free energy for the reversible insertion of the solutes in the bilayer is systematically assessed by evaluating dozens of separate sets of umbrella sampling

calculations for a total simulation time exceeding 400 μ s.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Computational Screening for Active Compounds Targeting Protein Sequences: Methodology and Experimental Validation

Fei Wang, Dongxiang Liu, Heyao Wang, Cheng Luo, Mingyue Zheng, Hong Liu, Weiliang Zhu, Xiaomin Luo, Jian Zhang, and Hualiang Jiang [Chinese Academy of Sciences]

J.Chem. Infor. and Mod. **51**, 2821–2828, 2011.

The three-dimensional (3D) structures of most protein targets have not been determined so far, with many of them not even having a known ligand, a truly general method to predict ligand–protein interactions in the absence of three-dimensional information would be of great potential value in drug discovery. Using the support vector machine (SVM) approach, we constructed a model for predicting ligand–protein interaction based only on the primary sequence of proteins and the structural features of small molecules.

A New Coarse-Grained Force Field for Membrane–Peptide Simulations

Zhe Wu, Qiang Cui, and Arun Yethiraj [University of Wisconsin, Madison]

J. Chem. Theor. and Comp. **7**, 3793–3802, 2011.

We present a new coarse-grained (CG) model for simulations of lipids and peptides. The model follows the same topology and parametrization strategy as the MARTINI force field but is based on our recently developed big multipole water (BMW) model for water (*J. Phys. Chem. B* **2010**, 114, 10524–10529). The new BMW-MARTINI force field reproduces many fundamental membrane properties and also yields improved energetics (when compared to the original MARTINI force-field) for the interactions between charged amino acids with lipid membranes, especially at the membrane–water interface.

Molecular Determinants of Ligand Binding Modes in the Histamine H₄ Receptor: Linking Ligand-Based Three-Dimensional Quantitative Structure–Activity Relationship (3D-QSAR) Models to in Silico Guided Receptor Mutagenesis Studies

Enade P. Istyastono, Saskia Nijmeijer, Herman D. Lim, Andrea van de Stolpe, Luc Roumen, Albert J. Kooistra, Henry F. Vischer, Iwan J. P. de Esch, Rob Leurs, and Chris de Graaf [VU University Amsterdam]

J.Med.Chem., **54**, 8136–8147, 2011.

The histamine H₄ receptor (H₄R) is a G protein-coupled receptor (GPCR) that plays an important role in inflammation. Similar to the homologous histamine H₃ receptor (H₃R), two acidic residues in the H₄R binding pocket, D^{3.32} and E^{5.46}, act as essential hydrogen bond acceptors of positively ionizable hydrogen bond donors in H₄R ligands. Given the symmetric distribution of these complementary pharmacophore features in H₄R and its ligands, different alternative ligand binding mode hypotheses have been proposed. The current study focuses on the elucidation of the molecular determinants of H₄R–ligand binding modes by combining 3D - QSAR, protein homology modeling, molecular dynamics simulations, and site-directed mutagenesis studies.

Effect of Galactosylceramide on the Dynamics of Cholesterol-Rich Lipid Membranes

Anette Hall, Tomasz Róg, and Ilpo Vattulainen [Tampere University of Technology]

J. Phys. Chem. B., **115**, 14424–14434, 2011.

We use atom-scale MD simulations to clarify the role of glycosphingolipids in the dynamics of cholesterol-rich lipid rafts. To this end, we consider lipid membranes that contain varying amounts of galactosylceramide (GalCer), sphingomyelin, cholesterol, and phosphatidylcholine. The results indicate that increasing the portion of GalCer molecules greatly slows down the lateral diffusion. Only 5–10 mol % of GalCer causes a decrease of almost an order of magnitude compared to corresponding membranes without GalCer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Thermodynamic Analysis of Protegrin-1 Insertion and Permeation through a Lipid Bilayer

Victor Vivcharuk and Yiannis N. Kaznessis [University of Minnesota, Minneapolis]

J. Phys. Chem. B., **115**, 14704–14712, 2011.

Molecular dynamics (MD) simulations are used to study the pathway for the insertion of the cationic antimicrobial peptide protegrin-1 (PG1) into mixed anionic lipid bilayers composed of palmitoyl-oleoyl-phosphatidylglycerol (POPG) and palmitoyl-oleoyl-phosphatidylethanolamine (POPE) in a 1:3 ratio (POPG/POPE). We calculate the potential of mean force (PMF) during the transfer of the peptide from the bulk aqueous phase to the transmembrane (TM) configuration using the adaptive biasing force (ABF) method. We find that the PMF has two energy minima separated by an energy barrier.

BSP-SLIM: A blind low-resolution ligand-protein docking approach using predicted protein structures

Hui Sun Lee and Yang Zhang [University of Michigan]

Proteins: Stru. Fun. & Bioinf. **80**, 93–110, 2012.

We developed BSP-SLIM, a new method for ligand–protein blind docking using low-resolution protein structures. For a given sequence, protein structures are first predicted by I-TASSER; putative ligand binding sites are transferred from holo-template structures which are analogous to the I-TASSER models; ligand–protein docking conformations are then constructed by shape and chemical match of ligand with the negative image of binding pockets. BSP-SLIM was tested on 71 ligand–protein complexes from the Astex diverse set where the protein structures were predicted by I-TASSER with an average RMSD 2.92 Å on the binding residues.

Protein Folding

Unraveling the Molecular Mechanism of Enthalpy Driven Peptide Folding by Polyol Osmolytes

Regina Gilman-Politi and Daniel Harries [The Hebrew University]

J. Chem. Theor. and Comp., **7**, 3816–3828, 2011.

Many polyols and carbohydrates serve in different organisms as protective osmolytes that help to stabilize proteins in their native, functional state, even under a variety of environmental stresses. However, despite their important role, much of the molecular mechanism by which these osmolytes exert their action remains elusive. We have recently shown experimentally that, although polyols and carbohydrates are excluded from protein and peptide interfaces, as also expected for the known entropic “crowding” mechanism, the osmolyte folding action can in fact primarily be enthalpic in nature. To follow this newly resolved enthalpically driven stabilization mechanism, we report here on molecular dynamics simulations of a model peptide that can fold in solution into a β -hairpin.

Protein Folding (Cont'd)

A Simple Mechanism Underlying the Effect of Protecting Osmolytes on Protein Folding

G. Saladino, M. Marenchino, S. Pieraccini, R. Campos-Olivas, M. Sironi [Universita' degli Studi di Milano], and F. L. Gervasio

J. Chem. Theor. and Comp., **7**, 3846–3852, 2011.

Osmolytes are small organic compounds that confer to the cell an enhanced adaptability to external conditions. Many osmolytes not only protect the cell from osmotic stress but also stabilize the native structure of proteins. While simplified models able to predict changes to protein stability are available, a general physicochemical explanation of the underlying microscopic mechanism is still missing. Here, we address this issue by performing very long all-atom MD simulations, free energy calculations, and experiments on a well-characterized mini-protein, the villin headpiece.

A Hybrid All-Atom Structure-Based Model for Protein Folding and Large Scale Conformational Transitions

Ludovico Sutto, Ilaria Mereu, and Francesco Luigi Gervasio [Spanish National Cancer Research Center]

J. Chem. Theor. and Comp., **7**, 4208–4217, 2011.

Structure-based models are successful at conjugating the essence of the energy landscape theory of protein folding with an easy and efficient implementation. Recently, their realm expanded beyond a single protein structure, and structure-based potentials have been used profitably to widely study complex conformational transitions. Here, we propose an all-atom model that merges a classical force field description of these local interactions with a structure-based long-range potential that takes into account the different conformations.

Protein-Nucleic acid Interactions

Exploration of the binding mode of α/β -type small acid soluble proteins (SASPs) with DNA

Yan Ge, Jiayan Wu, Jingfa Xiao [Beijing Institute of Genomics] and Jun Yu

J. Mol.Mod., **17**, 3183-3193, 2011.

The α/β -type small acid soluble proteins (SASPs) are a major factor in protecting the spores from being killed in bacteria. In this article, we perform a systematic phylogenetic analysis of the α/β -type SASP in the genus of *Geobacillus*, which indicates that the whole family can be divided into three groups. We choose one protein from each group as a representative and construct the tertiary structure of these proteins. In order to explore the mechanism of protecting DNA from damage, 15 ns molecular dynamics simulation for the four complexes of Gsy3 with DNA are performed.

Nucleic Acids

Nonspecific Transcription-Factor-DNA Binding Influences Nucleosome Occupancy in Yeast

Ariel Afek, Itamar Sela, Noa Musa-Lempel, David B. Lukatsky [Ben-Gurion University of the Negev]

Biophysical Journal. **101**, 2465-2475, 2011.

Quantitative understanding of the principles regulating nucleosome occupancy on a genome-wide level is a central issue in eukaryotic genomics. We perform a genome-wide computational analysis of the nonspecific transcription factor (TF)-DNA binding free-energy landscape and compare this landscape with experimentally determined nucleosome-binding preferences. We show that DNA regions with enhanced nonspecific TF-DNA binding are statistically significantly depleted of nucleosomes. We suggest therefore that the competition between TFs with histones for nonspecific binding to genomic sequences might be an important mechanism influencing nucleosome-binding preferences in vivo.

PDCD5-Regulated Cell Fate Decision after Ultraviolet-Irradiation-Induced DNA Damage

Changjing Zhuge, Ying Chang, Yanjun Li, Yingyu Chen, Jinzhi Lei [Tsinghua University]

Biophysical Journal. **101**, 2582-2591, 2011.

Programmed cell death 5 (PDCD5) is a human apoptosis-related molecule that is involved in both the cytoplasmic caspase-3 activity pathway (by regulating Bax translocation from cytoplasm to mitochondria) and the nuclear pathway (by interacting with Tip60). In this study, we developed a mathematical model of the PDCD5-regulated switching of the cell response from DNA repair to apoptosis after ultraviolet irradiation-induced DNA damage. We established the model by combining several hypotheses with experimental observations.

Sequence-Specific Mg^{2+} -DNA Interactions: A Molecular Dynamics Simulation Study

Weifeng Li, Lars Nordenskiöld, and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B., **115**, 14713–14720, 2011.

The effects of Mg^{2+} ions, in comparison with Na^+ ions, on DNA structure and conformational dynamics were studied by molecular dynamics simulations. Mg^{2+} ions, with a stable hydration shell consisting of six water molecules, interact with DNA mainly through hydrogen bond interactions, which are sensitive to the local environment. Mg^{2+} ions were found at the phosphate backbone and selectively in the major groove of G-C bases. The sequence-dependent specificity is of electrostatic nature and not caused by steric constraints.

Is DNA's Rigidity Dominated by Electrostatic or Nonelectrostatic Interactions?

Alexey Savelyev, Christopher K. Materese, and Garegin A. Papoian [University of North Carolina at Chapel Hill]

J. Am. Chem. Soc., **133**, 19290–19293, 2011.

Double-stranded DNA is among the stiffest biopolymers, whose bending propensity crucially influences many vital biological processes. It is not fully understood which among the two most likely forces, electrostatic self-repulsion or the compressive base pair stacking, plays a dominant role in determining the DNA's unique rigidity. Different theoretical and experimental studies led so far to contradictory results on this issue. In this Communication, we address this important question by means of Molecular Dynamics (MD) simulations using both atomistic and coarse-grained force fields.

Nucleic Acids (Cont'd)

Quantum-chemical study of interactions of trans-resveratrol with guanine-thymine dinucleotide and DNA-nucleobases

Damian Mikulski [A. Mickiewicz University ul], Małgorzata Szeląg and Marcin Molski

J. Mol.Mod., **17**, 3085-3102, 2011.

Trans-resveratrol, a natural phytoalexin present in red wine and grapes, has gained considerable attention because of its antiproliferative, chemopreventive and proapoptotic activity against human cancer cells. The accurate quantum-chemical computations based on the density functional theory (DFT) and ab initio second-order Møller-Plesset perturbation method (MP2) have been performed for the first time to study interactions of trans-resveratrol with guanine-thymine dinucleotide and DNA-derived nitrogenous bases: adenine, guanine, cytosine and thymine in vacuum and water medium.

Localization and anharmonicity of the vibrational modes for GC Watson–Crick and Hoogsteen base pairs

Attila Bende, Diana Bogdan, Cristina M. Muntean and Cristian Morari [National Institute for Research and Development of Isotopic and Molecular Technologies]

J. Mol.Mod., **17**, 3265-3274, 2011.

We present an ab initio study of the vibrational properties of cytosine and guanine in the Watson–Crick and Hoogsteen base pair configurations. The results are obtained by using two different implementations of the DFT method. We assign the vibrational frequencies to cytosine or to guanine using the vibrational density of states. Next, we investigate the importance of anharmonic corrections for the vibrational modes. In particular, the unusual anharmonic effect of the H⁺ vibration in the case of the Hoogsteen base pair configuration is discussed.

A-Minor Tertiary Interactions in RNA Kink-Turns. Molecular Dynamics and Quantum Chemical Analysis

Kamila Réblová, Judit E. Šponer, Naďa Špačková, Ivana Beššeová, and Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **115**, 13897–13910, 2011.

The RNA kink-turn is an important recurrent RNA motif, an internal loop with characteristic consensus sequence forming highly conserved three-dimensional structure. Functional arrangement of RNA kink-turns shows a sharp bend in the phosphodiester backbone. Among other signature interactions, kink-turns form A-minor interaction between their two stems. We carried out an extended set (~5 μs) of explicit-solvent molecular dynamics simulations of kink-turns to rationalize this structural/evolutionary pattern. The simulations were done using a net-neutral Na⁺ cation atmosphere (with ~0.25 M cation concentration) supplemented by simulations with either excess salt KCl atmosphere or inclusion of Mg²⁺.

Formation of N–N Cross-Links in DNA by Reaction of Radiation-Produced DNA Base Pair Diradicals: A DFT Study

Venkata Pottiboyina, Anil Kumar, and Michael D. Sevilla [Oakland University]

J. Phys. Chem. B., **115**, 15090–15097, 2011.

This study employs DFT (density functional theory) to investigate the formation of hydrazine-like (N–N) cross-linked structures between DNA base pair diradicals that are likely to result from the interaction of high linear energy transfer (LET) radiation, such as ion-beam radiation, with DNA. In our calculations, we generated the guanine (G), cytosine (C), adenine (A), and thymine (T) radicals by removing one hydrogen atom from an N–H bond involved in the normal base pairing. The radical species formed are those that naturally result from one-electron oxidation of the bases followed by deprotonation.

2. METHODOLOGY

Potentials and Parameters

Why the OPLS-AA Force Field Cannot Produce the Beta-Hairpin Structure of H1 Peptide in Solution When Comparing with the GROMOS 43A1 Force Field?

Zanxia Cao, Lei Liu, Jihua Wang [Shandong Provincial Key Laboratory of Functional Macromolecular Biophysics]

J. Biomol. Stru. and Dyn., **29**, 527-539, 2011.

The optimal combination of force field and water model is an essential problem that is able to increase molecular dynamics simulation quality for different types of proteins and peptides. In this work, an attempt has been made to explore the problem by studying H1 peptide using four different models based on different force fields, water models and electrostatic schemes. The driving force for H1 peptide conformation transition and the reason why the OPLS-AA force field cannot produce the β -hairpin structure of H1 peptide in solution while the GROMOS 43A1 force field can do were investigated by temperature replica exchange molecular dynamics simulation (T-REMD).

Quantum mechanically derived AMBER-compatible heme parameters for various states of the cytochrome P450 catalytic cycle

Kiumars Shahrokh, Anita Orendt, Garold S. Yost and Thomas E. Cheatham III [University of Utah]

J. Comp. Chem. **33**, 119–133, 2012.

Molecular mechanics (MM) methods are computationally affordable tools for screening chemical libraries of novel compounds for sites of P450 metabolism. One challenge for MM methods has been the absence of a consistent and transferable set of parameters for the heme within the P450 active site. We have developed and tested a consistent set of transferable MM parameters based on gas-phase QM calculations of two model systems of the heme—a truncated (T-HM) and a full (F-HM) for four states of the P450 catalytic cycle.

Molecular Dynamics

Computational network analysis of the anatomical and genetic organizations in the mouse brain

Shuiwang Ji [Old Dominion University]

Bioinformatics. **27**, 3293-3299, 2011.

The mammalian central nervous system (CNS) generates high-level behavior and cognitive functions. Elucidating the anatomical and genetic organizations in the CNS is a key step toward understanding the functional brain circuitry. We employ data reduction and network modeling techniques to explore the anatomical and genetic organizations in the mouse brain. First, to reduce the volume of data, we propose to apply tensor factorization techniques to reduce the data volumes. This tensor formulation treats the stack of 3D volumes as a 4D data array, thereby preserving the mouse brain geometry.

Molecular Dynamics (Cont'd)

Spontaneous Formation of Twisted A β ₁₆₋₂₂ Fibrils in Large-Scale Molecular-Dynamics Simulations

Mookyung Cheon, Iksoo Chang [Pusan National University], Carol K. Hall

Biophysical Journal. **101**, 2493-2501, 2011.

Protein aggregation is associated with fatal neurodegenerative diseases, including Alzheimer's and Parkinson's. Mapping out kinetics along the aggregation pathway could provide valuable insights into the mechanisms that drive oligomerization and fibrillization, but that is beyond the current scope of computational research. Here we trace out the full kinetics of the spontaneous formation of fibrils by 48 A β ₁₆₋₂₂ peptides, following the trajectories in molecular detail from an initial random configuration to a final configuration of twisted protofilaments with cross- β -structure. We accomplish this by performing large-scale MD simulations based on an implicit-solvent, intermediate-resolution protein model, PRIME20.

Hot and Crowded: New Insights into the Dynamics of Thermophilic Enzymes from Multiscale Modeling

Matthias Heyden, Douglas J. Tobias [University of California]

Biophysical Journal. **101**, 2553-2554, 2011.

Understanding how the amino acid sequence of a protein determines its three-dimensional structure, dynamics, and, ultimately, its biological function remains a biophysical problem. Adaptation to extreme environmental conditions, e.g., high temperatures, led to the evolution of thermophilic enzymes that are not only stable at temperatures beyond 60°C, but also exhibit their maximum activity at elevated temperatures. Studying thermophilic enzyme homologs from different species side-by-side enables an assessment of how moderate changes in sequence and structure alter the enzyme's properties toward higher thermostability and high activity

A Structural Perspective on the Dynamics of Kinesin Motors

Changbong Hyeon [Korea Institute for Advanced Study], José N. Onuchic

Biophysical Journal. **101**, 2749-2759, 2011.

Despite significant fluctuation under thermal noise, biological machines in cells perform their tasks with exquisite precision. Using molecular simulation of a coarse-grained model and theoretical arguments, we envisaged how kinesin, a prototype of biological machines, generates force and regulates its dynamics to sustain persistent motor action. A structure-based model, which can be versatile in adapting its structure to external stresses while maintaining its native fold, was employed to account for several features of kinesin dynamics along the biochemical cycle.

Link between Allosteric Signal Transduction and Functional Dynamics in a Multisubunit Enzyme: S-Adenosylhomocysteine Hydrolase

Yoonji Lee, Lak Shin Jeong, Sun Choi [Ewha Womans University], and Changbong Hyeon

J. Am. Chem. Soc., **133**, 19807-19815, 2011.

S-adenosylhomocysteine hydrolase (SAHH), a cellular enzyme that plays a key role in methylation reactions including those required for maturation of viral mRNA, is an important drug target in the discovery of antiviral agents. While targeting the active site is a straightforward strategy of enzyme inhibition, evidence of allosteric modulation of active site in many enzymes underscores the molecular origin of signal transduction. To study the link between the allosteric communication and functional dynamics of SAHHs, we performed Brownian dynamics simulations by building a coarse-grained model based on the holo and ligand-bound structures.

Molecular Dynamics (Cont'd)

Empirical formulation and parameterization of cation- π interactions for protein modeling

Qi-Shi Du [Guangxi Academy of Sciences], Si-Yu Long, Jian-Zong Meng and Ri-Bo Huang

J. Comp. Chem. **33**, 153–162, 2012.

Cation- π interaction is comparable and as important as other main molecular interaction types, such as hydrogen bond, electrostatic interaction, van der Waals interaction, and hydrophobic interaction. Cation- π interactions frequently occur in protein structures, because six (Phe, Tyr, Trp, Arg, Lys, and His) of 20 natural amino acids and all metallic cations could be involved in cation- π interaction. Cation- π interactions arise from complex physicochemical nature and possess unique interaction behaviors, which cannot be modeled and evaluated by existing empirical equations and force field parameters that are widely used in the molecular dynamics.

Quantum mechanically derived AMBER-compatible heme parameters for various states of the cytochrome P450 catalytic cycle

Kiumars Shahrokh, Anita Orendt, Garold S. Yost and Thomas E. Cheatham III [University of Utah]

J. Comp. Chem. **33**, 119–133, 2012.

Many of the existing molecular simulation tools require the efficient identification of the set of nonbonded interacting atoms. This is necessary, for instance, to compute the energy values or the steric contacts between atoms. Cell linked-lists can be used to determine the pairs of atoms closer than a given cutoff distance in asymptotically optimal time. Despite this long-term optimality, many spurious distances are anyway computed with this method. Therefore, several improvements have been proposed, most of them aiming to refine the volume of influence for each atom. Here, we suggest a different improvement strategy based on avoiding to fill cells with those atoms that are always at a constant distance of a given atom.

Monte Carlo

Sequential Monte Carlo multiple testing

Geir Kjetil Sandve [Oslo University Hospital], Egil Ferkingstad, and Ståle Nygård

Bioinformatics. **27**, 3235–3241, 2011.

In molecular biology, as in many other scientific fields, the scale of analyses is ever increasing. Often, complex Monte Carlo simulation is required, sometimes within a large-scale multiple testing setting. The resulting computational costs may be prohibitively high. We here present MCFDR, a simple, novel algorithm for false discovery rate (FDR) modulated sequential Monte Carlo (MC) multiple hypothesis testing. The algorithm iterates between adding MC samples across tests and calculating intermediate FDR values for the collection of tests.

Monte Carlo (Cont'd)

Accelerating molecular monte carlo simulations using distance and orientation-dependent energy tables: Tuning from atomistic accuracy to smoothed “coarse-grained” models

Steven Lettieri and Daniel M. Zuckerman [University of Pittsburgh]

J. Comp. Chem. **33**, 268–275, 2012.

Typically, the most time consuming part of any atomistic molecular simulation is the repeated calculation of distances, energies, and forces between pairs of atoms. However, many molecules contain nearly rigid multi-atom groups such as rings and other conjugated moieties, whose rigidity can be exploited to significantly speed-up computations. The availability of GB-scale random-access memory (RAM) offers the possibility of tabulation (precalculation) of distance- and orientation-dependent interactions among such rigid molecular bodies. Here, we perform an investigation of this energy tabulation approach for a fluid of atomistic—but rigid—benzene molecules at standard temperature and density.

QM and QM/MM

Adaptive-Partitioning Redistributed Charge and Dipole Schemes for QM/MM Dynamics Simulations: On-the-fly Relocation of Boundaries that Pass through Covalent Bonds

Soroosh Pezeshki and Hai Lin [University of Colorado Denver]

J. Chem. Theor. and Comp. **7**, 3625–3634, 2011.

Recently, Heyden, Lin, and Truhlar (*J. Phys. Chem. B* **2007**, 111, 2231–2241) formalized the adaptive-partitioning schemes for quantum mechanical and molecular mechanical (QM/MM) molecular dynamics simulations. The adaptive-partitioning schemes permit on-the-fly reclassification of atoms/groups as part of the QM or MM subsystems during dynamics simulations. Test simulations of argon atoms in a periodic box with dual-level MM potentials in the microcanonical ensemble demonstrated that the adaptive-partitioning schemes conserved energy and momentum, which is critical to ensure correct sampling of configuration spaces of desired ensembles.

A Multibox Splitting Scheme: Robust Approximation For ab Initio Molecular Dynamics

Stas M. Avdoshenko [Dresden University of Technology]

J. Chem. Theor. and Comp. **7**, 3872–3883, 2011.

In this work, the multibox (M-box) simulation scheme is introduced, which can be considered as a generalization of the QM/MM scheme for multifragment (molecular) systems. This scheme exploits the natural locality of multifragment molecular-based systems by mapping the system into force-coupled block subspaces. Where defined in this way, the entire system can be fully modeled under a quantum mechanical force field. This allows the description of each subspace explicitly by means of a robust electronic structure theory without the requirement for large computational resources. An adequate block-to-block coupling by means of shared subsystem fragments is applied to preserve the long-distance structural correlation in the system during a molecular dynamic (MD) simulation.

QM and QM/MM (Cont'd)

Accuracy of Density Functionals in the Prediction of Electronic Proton Affinities of Amino Acid Side Chains

Natércia F. Brás, Marta A. S. Perez, Pedro A. Fernandes, Pedro J. Silva, and Maria J. Ramos [Universidade do Porto]

J. Chem. Theor. and Comp., **7**, 3898–3908, 2011.

The ionization states of amino acids influence the structure, function, stability, solubility, and reactivity of proteins and are difficult to determine unambiguously by experimental means. Thus, it is very important to be able to determine them theoretically and with high reliability. We have analyzed how well DFT functionals, often used to characterize complex and large models such as proteins, describe the zero-point-exclusive proton affinity at 0 K, PA_{el}^{OK} , for the ionizable side chains of lysine (Lys), histidine (His), arginine (Arg), and aspartate (Asp^-) as well as the cysteine (Cys^-), serine (Ser^-), and tyrosine (Tyr^-) anions. The reference values PA_{el}^{OK} were determined at the very accurate CCSD(T)/CBS level.

QM/MM Studies of Hairpin Ribozyme Self-Cleavage Suggest the Feasibility of Multiple Competing Reaction Mechanisms

Vojtěch Mlýnský, Pavel Banáš, Nils G. Walter, Jiří Šponer [Academy of Sciences of the Czech Republic], and Michal Otyepka

J. Phys. Chem. B., **115**, 13911–13924, 2011.

The hairpin ribozyme is a prominent member of small ribozymes since it does not require metal ions to achieve catalysis. Guanine 8 (G8) and adenine 38 (A38) have been identified as key participants in self-cleavage and -ligation. We have carried out hybrid quantum-mechanical/molecular mechanical (QM/MM) calculations to evaluate the energy along several putative reaction pathways. The error of our DFT description of the QM region was tested and shown to be ~ 1 kcal/mol.

Deep UV Resonance Raman Spectroscopy of β -Sheet Amyloid Fibrils: A QM/MM Simulation

Hao Ren [University of California, Irvine], Jun Jiang, and Shaul Mukamel

J. Phys. Chem. B., **115**, 13955–13962, 2011.

We present a combined quantum mechanics and molecular mechanics study of the deep ultraviolet $\pi\pi^*$ resonance Raman spectra of β -sheet amyloid fibrils $A\beta_{34-42}$ and $A\beta_{1-40}$. Effects of conformational fluctuations are described using a Ramachandran angle map, thus avoiding repeated ab initio calculations. Experimentally observed effects of hydrogen–deuterium exchange are reproduced. We propose that the AmIII band redshift upon deuteration is caused by the loss of coupling between C_α -H bending and N-D bending modes, rather than by peptide bond hydration.

Comparative or Homology Modeling

Study of protein complexes via homology modeling, applied to cysteine proteases and their protein inhibitors

Özlem Tastan Bishop [Rhodes University] and Matthys Kroon

J. Mol. Mod., **17**, 3163–3172, 2011.

This paper develops and evaluates large-scale calculation of 3D structures of protein complexes by homology modeling as a promising new approach for protein docking. The complexes investigated were papain-like cysteine proteases and their protein inhibitors, which play numerous roles in human and parasitic metabolisms. The structural modeling was performed in two parts. For the first part (evaluation set), nine crystal structure complexes were selected, 1325 homology models of known complexes were rebuilt by various templates including hybrids, allowing an analysis of the factors influencing the accuracy of the models.

Ligand Docking

Structural Diversity and Changes in Conformational Equilibria of Biantennary Complex-Type N-Glycans in Water Revealed by Replica-Exchange Molecular Dynamics Simulation

Suyong Re, Naoyuki Miyashita, Yoshiki Yamaguchi, Yuji Sugita [RIKEN Advanced Science Institute]

Biophysical Journal. **101**, L44-L46, 2011.

Structural diversity of N-glycans is essential for specific binding to their receptor proteins. To gain insights into structural and dynamic aspects in atomic detail not normally accessible by experiment, we here perform extensive MD simulations of N-glycans in solution using the replica-exchange method. The simulations show that five distinct conformers exist in solution for the N-glycans with and without bisecting GlcNAc. Importantly, the population sizes of three of the conformers are drastically reduced upon the introduction of bisecting GlcNAc.

Bacterial Cytoplasm Production of an EGFP-Labeled Single-Chain Fv Antibody Specific for the HER2 Human Receptor

Alessio Lombardi, Giulio Gianese, Caterina Arcangeli, Patrizia Galeffi, Maria Sperandei [UTAGRI-GEN Unit]

J. Biomol. Stru. and Dyn., **29**, 425-439, 2011.

The human epidermal growth factor receptor 2 (HER2) is the main diagnostic marker of breast and ovary cancers. Here, to obtain a rapid and sensitive immunodiagnostic tool a single-chain antibody (scFv800E6) specific for the HER2 was fused to the N-terminus of the enhanced green fluorescent protein (EGFP) by a flexible linker. The soluble production of the novel scFv800E6-EGFP protein in the cytoplasm of *Escherichia coli* was investigated at different induction temperatures (25, 30 and 37°C); the intrinsic fluorescent properties and the binding activity to HER2 positive tumour cells of the fusion protein were analysed.

New Aryl Hydrocarbon Receptor Homology Model Targeted To Improve Docking Reliability

Ilaria Motto, Annalisa Bordogna, Anatoly A. Soshilov, Michael S. Denison, and Laura Bonati [Università degli Studi di Milano-Bicocca]

J.Chem. Infor. and Mod. **51**, 2868–2881, 2011.

The aryl hydrocarbon receptor (AhR) is a ligand-dependent, basic helix–loop–helix Per-ARNT-Sim (PAS) containing transcription factor that can bind and be activated by structurally diverse chemicals, including the toxic environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). As no experimentally determined structures of the AhR ligand binding domain (LBD) are available and previous homology models were only derived from apo template structures, we developed a new model based on holo X-ray structures of the hypoxia-inducible factor 2 α (HIF-2 α) PAS B domain, targeted to improve the accuracy of the binding site for molecular docking applications.

Discovery of Novel Checkpoint Kinase 1 Inhibitors by Virtual Screening Based on Multiple Crystal Structures

Yan Li, Dong Joon Kim, Weiya Ma, Ronald A. Lubet, Ann M. Bode, and Zigang Dong [University of Minnesota, Austin]

J.Chem. Infor. and Mod. **51**, 2904–2914, 2011.

Incorporating receptor flexibility is considered crucial for improvement of docking-based virtual screening. With an abundance of crystallographic structures freely available, docking with multiple crystal structures is believed to be a practical approach to cope with protein flexibility. Here we describe a successful application of the docking of multiple structures to discover novel and potent Chk1 inhibitors. Forty-six Chk1 structures were first compared in single structure docking by predicting the binding mode and recovering known ligands. Combinations of different protein structures were then compared by recovery of known ligands and an optimal ensemble of Chk1 structures were selected.

Ligand Docking (Cont'd)

The Ensemble Performance Index: An Improved Measure for Assessing Ensemble Pose Prediction Performance

Oliver Korb [Cambridge Crystallographic Data Centre], Patrick McCabe, and Jason Cole

J.Chem. Infor. and Mod. **51**, 2915–2919, 2011.

We present a theoretical study on the performance of ensemble docking methodologies considering multiple protein structures. We perform a theoretical analysis of pose prediction experiments which is completely unbiased, as we make no assumptions about specific scoring functions, search paradigms, protein structures, or ligand data sets. We introduce a novel interpretable measure, the ensemble performance index (EPI), for the assessment of scoring performance in ensemble docking, which will be applied to simulated and real data sets.

Crystal Structure-Based Virtual Screening for Fragment-like Ligands of the Human Histamine H₁ Receptor

Chris de Graaf, Albert J. Kooistra, Henry F. Vischer, Vsevolod Katritch, Martien Kuijer, Mitsunori Shiroishi, So Iwata, Tatsuro Shimamura, Raymond C. Stevens, Iwan J. P. de Esch, and Rob Leurs [VU University Amsterdam]

J.Med.Chem., **54**, 8195–8206, 2011.

The recent crystal structure determinations of druggable class A G protein-coupled receptors (GPCRs) have opened up excellent opportunities in structure-based ligand discovery for this pharmaceutically important protein family. We have developed and validated a customized structure-based virtual fragment screening protocol against the recently determined human histamine H₁ receptor (H₁R) crystal structure. The method combines molecular docking simulations with a protein–ligand interaction fingerprint (IFP) scoring method.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(2), January, 2012.

- 119–133 **Quantum mechanically derived AMBER-compatible heme parameters for various states of the cytochrome P450 catalytic cycle**, Kiumars Shahrokh, Anita Orendt, Garold S. Yost and Thomas E. Cheatham III [University of Utah]

See Methodology / Potentials and Parameters.

- 134–140 **Similarity recognition of molecular structures by optimal atomic matching and rotational superposition**, Benjamin Helmich and Marek Sierka [Humboldt-Universität zu Berlin]

An algorithm for similarity recognition of molecules and molecular clusters is presented which also establishes the optimum matching among atoms of different structures.

- 141–152 **Molecular dynamics simulation of hydrated DPPC monolayers using charge equilibration force fields**, Timothy R. Lucas, Brad A. Bauer, Joseph E. Davis and Sandeep Patel [University of Delaware]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 153–162 **Empirical formulation and parameterization of cation- π interactions for protein modeling**, Qi-Shi Du [Guangxi Academy of Sciences], Si-Yu Long, Jian-Zong Meng and Ri-Bo Huang

See Methodology / Molecular Dynamics.

- 163–169 **A Topological method for global optimization of clusters: Application to $(\text{TiO}_2)_n$ ($n = 1-6$)**, Lingli Tang, Linwei Sai, Jijun Zhao [Dalian University of Technology] and Ruifeng Qiu

A new topological method is presented to generate the isomer structures of compound clusters with well defined covalent bonds. This method, combined with density functional theory, has been used to perform global optimization of $(\text{TiO}_2)_n$ ($n = 1-6$) clusters.

- 170–174 **Verification of DFT-predicted hydrogen storage capacity of VC_3H_3 complex using molecular dynamics simulations**, Nitin Wadnerkar, Vijayanand Kalamse, Shyi-Long Lee and Ajay Chaudhari [Swami Ramanand Teerth Marathwada University]

Density functional theory (DFT) and Fourth-order Möller-Plesset (MP4) perturbation theory calculations are performed to examine the possibility of hydrogen storage in V-capped VC_3H_3 complex.

- 175–188 **Dynamics and mechanism of structural diffusion in linear hydrogen bond**, Sermsiri Chaiwongwattana, Mayuree Phonyiem, Viwat Vchirawongkwin, Supakit Prueksaaron and Kritsana Sagarik [Suranaree University of Technology]

Dynamics and mechanism of proton transfer in a protonated hydrogen bond (H-bond) chain were studied, using the $\text{CH}_3\text{OH}_2^+(\text{CH}_3\text{OH})_n$ complexes, $n = 1-4$, as model systems. The present investigations used B3LYP/TZVP calculations and Born-Oppenheimer MD (BOMD) simulations at 350 K to obtain characteristic H-bond structures, energetic and IR spectra of the transferring protons in the gas phase and continuum liquid.

- 189–202 **MATCH: An atom-typing toolset for molecular mechanics force fields**, Joseph D. Yesselman, Daniel J. Price, Jennifer L. Knight and Charles L. Brooks III [University of Michigan]

We introduce a toolset of program libraries collectively titled multipurpose atom-typer for CHARMM (MATCH) for the automated assignment of atom types and force field parameters for molecular mechanics simulation of organic molecules.

- 203–210 **Theoretical study on the reaction $\text{CX}_3 + \text{SiH}(\text{CH}_3)_3$ ($\text{X} = \text{H}, \text{F}$)**, Hui Zhang, Liu Yang, Jing-Yao Liu and Ze-Sheng Li [Harbin Institute of Technology]

Theoretical investigations are carried out on the multiple-channel reactions, $\text{CH}_3 + \text{SiH}(\text{CH}_3)_3 \rightarrow \text{products}$ and $\text{CF}_3 + \text{SiH}(\text{CH}_3)_3 \rightarrow \text{products}$.

- 211–219 **Theoretical investigation on redox-switchable second-order nonlinear optical responses of push–pull $\text{Cp}^*\text{CoEt}_2\text{C}_2\text{B}_4\text{H}_3$ -expanded (metallo)porphyrins**, Nana Ma, Chunguang Liu, Yongqing Qiu, Shiling Sun and Zhongmin Su [Northeast Normal University]

The second-order nonlinear optical (NLO) properties of the $\text{Cp}^*\text{Co}(\text{C}_2\text{H}_5)_2\text{C}_2\text{B}_4\text{H}_3$ -expanded (metallo)porphyrins ($\text{Cp}^* = \text{C}_5\text{Me}_5$) have been investigated by using ab initio RHF and density functional theory (DFT) methods.

- 220–230 **Mechanism for the reaction of 2-naphthol with N-methyl-N-phenyl-hydrazine suggested by the density functional theory investigations**, Jie Ying Gao, Cheng Hua Zhang, Mei Ming Luo, Chan Kyung Kim, Wei Chu and Ying Xue [Sichuan University]

For the first time the computed mechanisms for the novel reaction of 2-naphthol with N-methyl-N-phenylhydrazine, leading to 1-amino-2-naphthol (Tang et al., J Am Chem Soc 2008, 130, 5840), have been investigated using the density functional theory.

- 231–236 **An effective method for accurate prediction of the first hyperpolarizability of alkalides**, Jia-Nan Wang, Hong-Liang Xu, Shi-Ling Sun, Ting Gao, Hong-Zhi Li, Hui Li and Zhong-Min Su [Northeast Normal University]

The proper theoretical calculation method for nonlinear optical (NLO) properties is a key factor to design the excellent NLO materials. Yet it is a difficult task to obtain the accurate NLO property of large scale molecule. In present work, an effective intelligent computing method, as called extreme learning machine-neural network (ELM-NN), is proposed to predict accurately the first hyperpolarizability (β_0) of alkalides from low-accuracy first hyperpolarizability.

Journal of Computational Chemistry, 33 (3), January, 2012.

- 239–246 **A possible overestimation of the effect of acetylation on lysine residues in KQ mutant analysis,** Hirofumi Fujimoto [National Institute of Infectious Diseases, Shinjuku-ku], Mariko Higuchi, Manabu Koike, Hirotaka Ode, Miroslav Pinak, Juraj Kotulic Bunta, Toshiyuki Nemoto, Takashi Sakudoh, Naoko Honda, Hideaki Maekawa, Kimiaki Saito and Kozo Tsuchida

Acetylation of lysine residues, one of the most common protein post-transcriptional modifications, is thought to regulate protein affinity with other proteins or nucleotides. Experimentally, the effects of acetylation have been studied using recombinant mutants in which lysine residues (K) are substituted with glutamine (Q) as a mimic of acetyl lysine (KQ mutant), or with arginine (R) as a mimic of nonacetylated lysine (KR mutant).

- 247–258 **A computational chemist approach to gas sensors: Modeling the response of SnO₂ to CO, O₂, and H₂O Gases,** Jean-Marie Duc  r  , Anne Hemeryck [CNRS, LAAS], Alain Est  ve, Mehdi Djafari Rouhani, Georges Landa, Philippe M  nini, Cyril Tropis, Andr   Maisonnat, Pierre Fau and Bruno Chaudret

A general bottom-up modeling strategy for gas sensor response to CO, O₂, H₂O, and related mixtures exposure is demonstrated.

- 259–267 **SPINE X: Improving protein secondary structure prediction by multistep learning coupled with prediction of solvent accessible surface area and backbone torsion angles,** Eshel Faraggi, Tuo Zhang, Yuedong Yang, Lukasz Kurgan and Yaoqi Zhou [Indiana University Purdue University]

Accurate prediction of protein secondary structure is essential for accurate sequence alignment, three-dimensional structure modeling, and function prediction. The accuracy of ab initio secondary structure prediction from sequence, however, has only increased from around 77 to 80% over the past decade. Here, we developed a multistep neural-network algorithm by coupling secondary structure prediction with prediction of solvent accessibility and backbone torsion angles in an iterative manner.

- 268–275 **Accelerating molecular monte carlo simulations using distance and orientation-dependent energy tables: Tuning from atomistic accuracy to smoothed “coarse-grained” models,** Steven Lettieri and Daniel M. Zuckerman [University of Pittsburgh]

See Methodology / Monte Carlo.

- 276–285 **A new approximate method for the stochastic simulation of chemical systems: The representative reaction approach,** Shantanu Kadam and Kumar Vanka [National Chemical Laboratory, Dr. Homi Bhabha Road]

We have developed two new approximate methods for stochastically simulating chemical systems. The methods are based on the idea of representing all the reactions in the chemical system by a single reaction, i.e., by the “representative reaction approach” (RRA). Discussed in the article are the concepts underlying the new methods along with flowchart with all the steps required for their implementation.

- 286–293 **Analysis of lipid surface area in protein–membrane systems combining voronoi tessellation and monte carlo integration methods,** Takaharu Mori, Fumiko Ogushi and Yuji Sugita [RIKEN Quantitative Biology Center]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 294–300 **Rigid-CLL: Avoiding constant-distance computations in cell linked-lists algorithms**, V. Ruiz de Angulo [Institut de Robòtica i Informàtica Industrial], J. Cortés and J. M. Porta

See Methodology / Molecular Dynamics.

- 301–310 **QM/MM refinement and analysis of protein bound retinoic acid**, Xue Li, Zheng Fu and Kenneth M. Merz Jr. [University of Florida]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 311–318 **The stability of small helical gold nanorods: A relativistic density functional study**, Xiao-Jing Liu, Ian Hamilton [Wilfrid Laurier University], Robert P. Krawczyk and Peter Schwerdtfeger

Multistrand 7-1 helical Au₂₄, Au₃₂, and Au₄₀ structures with three, four, and five gold atoms in the central strand and 21, 28, and 35 gold atoms in the coaxial tube are investigated using relativistic density functional theory.

- 319–330 **Theoretical investigation of the ethylene dimer: Interaction energy and dipole moment**, Yulia N. Kalugina [Tomsk State University], Victor N. Cherepanov, Mikhail A. Buldakov, Natalia Zvereva-Loëte and Vincent Boudon

The interaction potential energy and the interaction-induced dipole moment surfaces of the van der Waals C₂H₄-C₂H₄ complex has been calculated for a broad range of intermolecular separations and configurations in the approximation of rigid interacting molecules.

Journal of Molecular Modeling, 17 (12), December, 2011.

- 3027-3038 **Effects of nanoparticles on the compatibility of PEO-PMMA block copolymers**, Dan Mu [Zaozhuang University], Jian-Quan Li, Wei-Dong Li and Song Wang

The compatibility of six kinds of designed poly(ethylene oxide)-block-poly(methyl methacrylate) (PEO-b-PMMA) copolymers was studied at 270, 298 and 400 K via mesoscopic modeling.

- 3039-3046 **Structure and electronic properties of Alq3 derivatives with electron acceptor/donor groups at the C4 positions of the quinolate ligands: a theoretical study**, Joshi Laxmikanth Rao [Indian Institute of Chemical Technology] and Kotamarthi Bhanuprakash

The molecular structures of the ground (S0) and first singlet excited (S1) states of Alq3 derivatives in which pyrazolyl and 3-methylpyrazolyl groups are substituted at the C4 positions of the 8-hydroxyquinolate ligands as electron acceptors, and piperidinyl and N-methylpiperazinyl groups are substituted at the same positions as electron donors, have been optimized using the B3LYP/6-31G* and CIS/6-31G* methods, respectively.

- 3047-3056 **Prediction of a new surface binding pocket and evaluation of inhibitors against huntingtin interacting protein 14: an insight using docking studies**, Shipra Gupta [Biotech Park, Sector-G Jankipuram, Lucknow], Gauri Misra, Mohan C. Pant and Prahlad Kishor Seth

Protein—protein interactions play an important role in regulating the expression of huntingtin protein (htt). . In the present study, an attempt has been made to explore the potential of several known Huntington inhibitors to inhibit HIP14. The docking studies have resulted in the identification of a novel binding site for these inhibitors distinct from the previously known ankyrin repeat domain.

- 3057-3062 **High pressure phase transition and elastic properties of covalent heavy rare-earth Antimonides**, Purvee Bhardwaj [Barkatullah University] and Sadhna Singh

In the present paper, we report an investigation into the high-pressure structural phase transition of rare earth antimonides (DySb and ErSb). A modified interaction potential model (MIPM) (including the covalency effect) has been developed.

- 3063-3073 **In silico identification of viper phospholipaseA2 inhibitors: validation by in vitro, in vivo studies**, Amit Nargotra, Sujata Sharma, Mohd Iqbal Alam, Surrinder Koul [Indian Institute of Integrative Medicine], Zabeer Ahmed and Asha Bhagat, et al.

See Applications / Medicinal Chemmistry and Drug Design.

- 3075-3084 **Integrative computational protocol for the discovery of inhibitors of the Helicobacter pylori nickel response regulator (NikR)**, Aldo Segura-Cabrera [Boulevard del Maestro esquina Elías Piña], Xianwu Guo, Arturo Rojo-Domínguez and Mario A. Rodríguez-Pérez

See Applications / Medicinal Chemmistry and Drug Design.

- 3085-3102 **Quantum-chemical study of interactions of trans-resveratrol with guanine-thymine dinucleotide and DNA-nucleobases**, Damian Mikulski [A. Mickiewicz University ul], Małgorzata Szelać and Marcin Molski

See Applications / Nucleic Acids.

- 3103-3115 **Long range molecular dynamics study of regulation of eukaryotic glucosamine-6-phosphate synthase activity by UDP-GlcNAc**, Aleksandra Miszkiewicz, Marek Wojciechowski [Gdansk University of Technology] and Sławomir Milewski

See Applications / Enzyme Catalysis.

- 3117-3128 **Effect of metal Ions (Ni²⁺, Cu²⁺ and Zn²⁺) and water coordination on the structure of L-phenylalanine, L-tyrosine, L-tryptophan and their zwitterionic forms**, Milan Remko [Comenius University Bratislava], Daniel Fitz, Ria Broer and Bernd Michael Rode

Methods of quantum chemistry have been applied to double-charged complexes involving the transition metals Ni²⁺, Cu²⁺ and Zn²⁺ with the aromatic amino acids (AAA) phenylalanine, tyrosine and tryptophan. The effect of hydration on the relative stability and geometry of the individual species studied has been evaluated within the supermolecule approach.

- 3129-3149 **Molecular dynamics simulation of the Staphylococcus aureus YsxC protein: molecular insights into ribosome assembly and allosteric inhibition of the protein**, Amit Goyal, Kannan Muthu, Manivel Panneerselvam, Anil Kumar Pole and Krishna Ramadas [Pondicherry University]

See Applications / Ligand Binding.

- 3151-3162 **A theoretical thermodynamic investigation of cascade reactions in dinuclear octa-azacryptates involving carbon dioxide**, Morad M. El-Hendawy, Niall J. English [University College Dublin] and Damian A. Mooney

This paper investigates the thermodynamics of gas-phase CO₂ cascade uptake-reactions in the form of carbonate or monomethylcarbonate anions in the host cavity of various dinuclear octa-azacryptates of m-CH₂C₆H₄CH₂ and 2,5-furano-spaced hosts, L 1 and L 2 cryptands, using density functional theory (DFT).

- 3163-3172 **Study of protein complexes via homology modeling, applied to cysteine proteases and their protein inhibitors**, Özlem Tastan Bishop [Rhodes University] and Matthys Kroon

See Methodology / Homology Modeling.

- 3173-3181 **Theoretical mechanistic study of the reaction of the methylidyne radical with methylacetylene**, Lili Zhang [Jilin University], Hui-ling Liu, Guang-Hui Yang, Xu-ri Huang and Yan Li, et al.

A detailed doublet potential energy surface for the reaction of CH with CH₃CCH is investigated at the B3LYP/6-311G(d,p) and G3B3 (single-point) levels. Various possible reaction pathways are probed.

- 3183-3193 **Exploration of the binding mode of α/β -type small acid soluble proteins (SASPs) with DNA**, Yan Ge, Jiayan Wu, Jingfa Xiao [Beijing Institute of Genomics] and Jun Yu

See Applications / Protein-Nucleic Acids interactions.

- 3195-3207 **Aggregation of Kanamycin A: dimer formation with physiological cations**, Johannes M. Dieterich, Ulrich Gerstel, Jens-Michael Schröder and Bernd Hartke [Christian-Albrechts-Universität]

Global cluster geometry optimization has focused so far on clusters of atoms or of compact molecules. We are demonstrating here that present-day techniques also allow to globally optimize clusters of extended, flexible molecules, and that such studies have immediate relevance to experiment.

- 3209-3217 **Formation of the Vilsmeier-Haack complex: the performance of different levels of theory**, Gül Altınbaş Özpınar, Dieter E. Kaufmann and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg]

Because of discrepancies in the available experimental data, an extensive theoretical investigation of the formation of the Vilsmeier-Haack (VH) complex has been carried out.

- 3219-3228 **Atomistic modeling of parylene-metal interactions for surface micro-structuring**, Alex V. Vasenkov [CFD Research Corporation]

Many applications, ranging from neural prosthetics and cardiac rhythm management systems to organics-based flexible display, can benefit from the engineering of parylene-metal-parylene structures via selective deposition. We used the quantum semiempirical Hamiltonian (QSH) solver coupled to a molecular dynamic (MD) model, which is particularly suited to study parylene-metal interactions due to its ability to determine the different pathways of the transformations involving making and breaking of chemical and physical bonds.

- 3229-3239 **Consequence of one-electron oxidation and one-electron reduction for aniline**, Ewa D. Raczynska [Warsaw University of Life Sciences], Tomasz M. Stępniewski and Katarzyna Kolczyńska

Quantum-chemical calculations were performed for all possible isomers of neutral aniline and its redox forms, and intramolecular proton-transfer (prototropy) accompanied by π -electron delocalization was analyzed.

- 3241-3250 **A combined molecular modeling study on a series of pyrazole/isoxazole based human Hsp90 α inhibitors**, Ying Yang, Huanxiang Liu, Juan Du, Jin Qin and Xiaojun Yao [Lanzhou University]

See Applications / QSAR.

- 3251-3255 **Designing molecular devices by altering bond lengths**, Vijay Lamba [HCTM Kaithal], Suman J. Wilkinson and Charu Arora

The work focuses on a theoretical approach to investigating the electric field (EF) dependence of bond-length alternation, the geometric and electronic structures of molecular wires used in the design of molecular electronic devices, the EF dependence of SCF energy, and the spatial distribution of the frontier orbitals of the molecular wires.

- 3257-3263 **Aromaticity and kinetic stability of fullerene C₃₆ isomers and their molecular ions**, Ablikim Kerim [Xinjiang University]

The aromatic character of fullerene C₃₆ isomers was examined by the Hess-Schaad resonance energy (HSRE), topological resonance energy (TRE) and the percentage topological resonance energy (%TRE) models.

- 3265-3274 **Localization and anharmonicity of the vibrational modes for GC Watson–Crick and Hoogsteen base pairs**, Attila Bende, Diana Bogdan, Cristina M. Muntean and Cristian Morari [National Institute for Research and Development of Isotopic and Molecular Technologies]

See Applications / Nucleic Acids.

- 3275-3288 **Complexation of alkali metal cations by crown-ether type podands with applications in solvent extraction: insights from quantum chemical calculations**, Mário Valente, Sérgio Filipe Sousa, Alexandre L. Magalhães [Faculdade de Ciências da Universidade do Porto] and Cristina Freire

The complexation behavior of nine polyether type podands with a varying number of oxygen donor atoms (4–10) towards the alkali metal cations Li⁺, Na⁺ and K⁺ was studied by quantum chemical methods at the DFT-B3LYP level of theory using the all-electron split-valence 6-311++G(d,p) basis set.

- 3289-3297 **Probing ¹³C chemical shielding tensors in cryptolepine and two bromo-substituted analogs for antiplasmodial activity**, Hadi Behzadi [Tarbiat Moallem University], Mohamad Reza Talei Babil Olyai and David van der Spoel

Density functional theory calculations were applied to investigate ^{13}C chemical shielding tensors in cryptolepine and its bromo-substituted analogs, 2-bromocryptolepine and 2,7-dibromocryptolepine.

- 3299-3308 **Adsorption and spin state properties of Cr, Ni, Mo, and Pt deposited on Li^+ and Na^+ monovalent cation impurities of MgO (001) surface: DFT calculations**, Ahmad S. Shalabi [Benha University], Mervat M. Assem and Kamal A. Soliman

We have analyzed, by means of density functional theory calculations and the embedded cluster model, the adsorption and spin-state properties of Cr, Ni, Mo, and Pt deposited on a MgO crystal. We considered deposition at the Mg^{2+} site of a defect-free surface and at Li^+ and Na^+ sites of impurity-containing surfaces.

- 3309-3318 **Halogen bond tunability I: the effects of aromatic fluorine substitution on the strengths of halogen-bonding interactions involving chlorine, bromine, and iodine**, Kevin E. Riley [University of Puerto Rico], Jane S. Murray, Jindřich Fanfrlík, Jan Řezáč and Ricardo J. Solá, et al.

In the past several years, halogen bonds have been shown to be relevant in crystal engineering and biomedical applications. One of the reasons for the utility of these types of noncovalent interactions in the development of, for example, pharmaceutical ligands is that their strengths and geometric properties are very tunable. In this study we investigate halogen-bonding interactions involving aromatically-bound halogens (Cl, Br, and I) and a carbonyl oxygen.

- 3319-3323 **Analytical evaluation of Coulomb potential generated by multielectron molecule at arbitrary positions in space using one-range addition theorems of Slater type orbitals**, Israfil I. Guseinov [Onsekiz Mart University]

By the use of unsymmetrical one-range addition theorems for Slater type orbitals (STO) and Coulomb potential introduced by the author, the analytical formulae in terms of two- and three-center nuclear attraction integrals, and linear combination coefficients of molecular orbitals are derived for the potential produced by the charges of molecule.

- 3325-3332 **Homology modeling and in silico screening of inhibitors for the substrate binding domain of human Siah2: implications for hypoxia-induced cancers**, Gopalsamy Anupriya, Kothapalli Roopa, S. Basappa, Yap Seng Chong and Loganath Annamalai [National University of Singapore]

See Applications / Homology Modeling.

4. ADDRESSES OF PRINCIPAL AUTHORS

The production sites for the corresponding or principal authors are given in brackets in the citations. When not designated by the publisher, the first author is assumed to be the principal. Current addresses are listed here.

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About 151 Papers from over 30 Journals are cited.

1	APPLICATIONS (118)	Page 2	
1.1	Small Molecules (31)		
	General and Model Systems	Page 2	QSAR Page 6
	Water and Solvation	Page 2	Carbon Nanoparticles Page 8
	Med. Chem. And Drug Design	Page 3	Crystal Growth Page 10
1.2	Biopolymers (87)		
	Bioinformatics and Cheminformatics	Page 10	Ligand Binding Page 20
	Protein Secondary Structure	Page 11	Enzyme Catalysis Page 22
	Comparative or Homology Modeling	Page 11	Membrane Proteins Page 24
	Protein Conformational Analysis	Page 13	Protein Folding Page 27
	Protein Dynamics	Page 14	Nucleic Acids Page 29
	Free Energy Calculations	Page 19	
1.3	Polymers		
1.4	Surfaces, Catalysts and Material	Page 33	
2	METHODOLOGY (33)	Page 27	
	QSAR	Page 33	Free Energy Perturbations Page 37
	Potentials and Parameters	Page 34	QM & QM/MM Page 38
	Molecular Dynamics	Page 35	Comparative or Homology Page 40
	Monte Carlo Simulation	Page 36	Ligand Docking Page 40
3	JOURNAL REVIEWS (5)	Page 41	
	Journal of Molecular Graphics and Modeling, 29 (5), January, 2011.		
	Journal of Computational Chemistry, 32 (3), February, 2011.		
	Journal of Computational Chemistry, 32 (4), March, 2011.		
	Journal of Molecular Modeling, 17(1), January, 2011.		
	Journal of Molecular Modeling, 17(2), february, 2011.		
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 55	
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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Molecular simulations of confined liquids: An alternative to the grand canonical Monte Carlo simulations

Aziz Ghoufi [Université Rennes 1], Denis Morineau, Ronan Lefort, Ivanne Hureau, Leila Hennous, Haochen Zhu, Anthony Szymczyk, Patrice Malfreyt, and Guillaume Maurin

Jou. Chem. Phys., **134**, 074104, 2011.

Commonly, the confinement effects are studied from the grand canonical Monte Carlo (GCMC) simulations from the computation of the density of liquid in the confined phase. The GCMC modeling and chemical potential (μ) calculations are based on the insertion/deletion of the real and ghost particle, respectively. At high density, *i.e.*, at high pressure or low temperature, the insertions fail from the Widom insertions while the performing methods as expanded method or perturbation approach are not efficient to treat the large and complex molecules. To overcome this problem we use a simple and efficient method to compute the liquid's density in the confined medium.

Water and Solvation

Calculation of Local Water Densities in Biological Systems: A Comparison of Molecular Dynamics Simulations and the 3D-RISM-KH Molecular Theory of Solvation

Martin C. Stumpe, Nikolay Blinov, David Wishart, Andriy Kovalenko, and Vijay S. Pande [Stanford University]

J. Phys. Chem. B., **115**, 319–328, 2011.

It is highly instructive to study the local water density around solutes in cellular systems, particularly when solvent-mediated forces such as the hydrophobic effect are relevant. We here compare the calculation of local water densities with two different methods: MD simulations and the three-dimensional reference interaction site model with the Kovalenko–Hirata closure (3D-RISM-KH). In particular, we investigate the convergence of the local water density to assess the required simulation times for different levels of resolution.



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Medicinal Chemistry and Drug Design

Virtual screening based identification of novel small-molecule inhibitors targeted to the HIV-1 capsid

Francesca Curreli, Hongtao Zhang, Xihui Zhang, Ilya Pyatkin, Zagorodnikov Victor, Andrea Altieri, Asim K. Debnath [Lindsley F. Kimball Research Institute of the New York Blood Center]

Bioorg. and Med.Chem., **19**, 77-90, 2011.

The hydrophobic cavity of the C-terminal domain (CTD) of HIV-1 capsid has been recently validated as potential target for antiviral drugs by peptide-based inhibitors; however, there is no report yet of any small molecule compounds that target this hydrophobic cavity. In order to fill this gap and discover new classes of ant-HIV-1 inhibitors, we undertook a docking-based virtual screening and subsequent analog search, and medicinal chemistry approaches to identify small molecule inhibitors against this target.

Design, synthesis and biological evaluation of small molecule inhibitors of CD4-gp120 binding based on virtual screening

Judith M. LaLonde [Bryn Mawr College], Mark A. Elban, Joel R. Courter, Akihiro Sugawara, Takahiro Soeta, Navid Madani, Amy M. Princiotta, Young Do Kwon, Peter D. Kwong, Arne Schön, Ernesto Freire, Joseph Sodroski, Amos B. Smith III

Bioorg. and Med.Chem., **19**, 91-101, 2011.

The low-molecular-weight compound JRC-II-191 inhibits infection of HIV-1 by blocking the binding of the HIV-1 envelope glycoprotein gp120 to the CD4 receptor and is therefore an important lead in the development of a potent viral entry inhibitor. Reported here is the use of two orthogonal screening methods, gold docking and ROCS shape-based similarity searching, to identify amine-building blocks that, when conjugated to the core scaffold, yield novel analogs that maintain similar affinity for gp120.

Molecular modeling based approach, synthesis and in vitro assay to new indole inhibitors of hepatitis C NS3/4A serine protease

Nasser S.M. Ismail [Ain Shams University], Masao Hattori

Bioorg. and Med.Chem., **19**, 374-383, 2011.

In an attempt to identify potential HCV NS3 protease inhibitors lead compounds, a series of novel indoles (**10a-g**) was designed. Molecular modeling study, including fitting to a 3D-pharmacophore model of the designed molecules (**10a-g**), with HCV NS3 protease hypothesis using catalyst program was fulfilled. Also, the molecular docking into the NS3 active site was examined using Discovery Studio 2.5 software. Several compounds showed significant high simulation docking score and fit values.

Computational approach to the identification of novel Aurora-A inhibitors

Mohammad Neaz Morshed, Yong Seo Cho, Seon Hee Seo, Ki-Cheol Han, Eun Gyeong Yang, Ae Nim Pae [Korea Institute of Science and Technology]

Bioorg. and Med.Chem., **19**, 907-916, 2011.

Aurora kinase A has been emerging as a key therapeutic target for the design of anticancer drugs. For the purpose of finding biologically active and novel compounds and providing new ideas for drug-design, we performed virtual screening using commercially available databases. A three-dimensional common feature pharmacophore model was developed with the HipHop program provided in the Catalyst software package, and this model was used as a query for screening the databases.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of curcumin derivatives as human glyoxalase I inhibitors: A combination of biological evaluation, molecular docking, 3D-QSAR and molecular dynamics simulation studies

Minggui Yuan, Minxian Luo, Yao Song, Qiu Xu, Xiaofeng Wang, Yi Cao, Xianzhang Bu, Yanliang Ren [Central China Normal University], Xiaopeng Hu

Bioorg. and Med.Chem., **19**, 1189-1196, 2011.

Several recent developments suggest that the human glyoxalase I (GLO I) is a potential target for anti-tumor drug development. In present study, a series of curcumin derivatives with high inhibitory activity against human GLO I were discovered. Inhibition constant (K_i) values of compounds **8**, **9**, **10**, **11** and **13** to GLO I are 4.600 μ M, 2.600 μ M, 3.200 μ M, 3.600 μ M and 3.600 μ M, respectively. To elucidate the structural features of potent inhibitors, docking-based three-dimensional structure-activity relationship (3D-QSAR) analyses were performed.

Prediction of drug intestinal absorption by new linear and non-linear QSPR

Alan Talevi, Mohammad Goodarzi, Erlinda V. Ortiz, Pablo R. Duchowicz [Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas INIFTA], Carolina L. Bellera, Guido Pesce, Eduardo A. Castro, Luis E. Bruno-Blanch

European J. of Med. Chem., **46**, 218-228, 2011.

In order to minimize the high attrition rate that usually characterizes drug research and development projects, current medicinal chemists aim to characterize both pharmacological and ADME profiles at the beginning of drug R&D initiatives. Thus, the development of ADME High-Throughput Screening in vitro and in silico ADME models has become an important growing research area. Here we present new linear and non-linear predictive QSPR models to predict the human intestinal absorption rate, which are derived from a medium sized, balanced and diverse training set of organic compounds.

Ligand - based virtual screening procedure for the prediction and the identification of novel β -amyloid aggregation inhibitors using Kohonen maps and Counterpropagation Artificial Neural Networks

Antreas Afantitis [NovaMechanics Ltd], Georgia Melagraki, Panayiotis A. Koutentis, Haralambos Sarimveis, George Kollias

European J. of Med. Chem., **46**, 497-508, 2011.

In this work we have developed an in silico model to predict the inhibition of β -amyloid aggregation by small organic molecules. In particular we have explored the inhibitory activity of a series of 62 N-phenylantranilic acids using Kohonen maps and Counterpropagation Artificial Neural Networks. The effects of various structural modifications on biological activity are investigated and novel structures are designed using the developed in silico model. More specifically a search for optimized pharmacophore patterns by insertions, substitutions, and ring fusions of pharmacophoric substituents of the main building block scaffolds is described.

Synthesis, molecular docking and binding studies of selective serotonin transporter inhibitors

Susanna Nencetti [Università di Pisa], Maria R. Mazzoni, Gabriella Ortore, Annalina Lapucci, Janette Giuntini, Elisabetta Orlandini, Irene Banti, Elisa Nuti, Antonio Lucacchini, Gino Giannaccini, Armando Rossello

European J. of Med. Chem., **46**, 825-834, 2011.

With the aim of obtaining compounds possessing high SERT selectivity, in the present work we synthesized and studied the inhibition of serotonin (SERT), dopamine (DAT) and norepinephrine (NET) transporters by docking studies and experimental binding measurements of a series of 4-(aryl)piperidin-3-one O-4-benzyl oxime hydrochlorides (**1-10**) of both E and Z configuration. E configuration compounds showed high SERT binding affinities (K_i = 10-98 nM) and high SERT selectivities over both NET and DAT.

Medicinal Chemistry and Drug Design (Cont'd)

Virtual screening studies on HIV-1 reverse transcriptase inhibitors to design potent leads

S. Vadivelan [GVK Biosciences Private Limited], T.N. Deeksha, S. Arun, Pavan Kumar Machiraju, Rambabu Gundla, Barij Nayan Sinha, Sarma A.R.P. Jagarlapudi

European J. of Med. Chem., **46**, 851-859, 2011.

The purpose of this study is to identify novel and potent inhibitors against HIV-1 reverse transcriptase (RT). The crystal structure of the most active ligand was converted into a feature-shaped query. This query was used to align molecules to generate statistically valid 3D-QSAR ($r^2 = 0.873$) and Pharmacophore models (HypoGen). The best HypoGen model consists of three Pharmacophore features (one hydrogen bond acceptor, one hydrophobic aliphatic and one ring aromatic) and further validated using known RT inhibitors.

Using Computer-aided Drug Design and Medicinal Chemistry Strategies in the Fight Against Diabetes

Evandro P. Semighini, Jonathan A. Resende, Peterson de Andrade, Pedro A. B. Morais, Ivone Carvalho, Carlton A. Taft [Universidade de São Paulo], Carlos H. T. P. Silva

J. Biomol. Stru. and Dyn., **28**, 787-796, 2011.

The aim of this work is to present a simple, practical and efficient protocol for drug design, in particular Diabetes, which includes selection of the illness, good choice of a target as well as a bioactive ligand and then usage of various computer aided drug design and medicinal chemistry tools to design novel potential drug candidates in different diseases. We have selected the validated target dipeptidyl peptidase IV (DPP-IV), whose inhibition contributes to reduce glucose levels in type 2 diabetes patients.

Discovery of new β -D-galactosidase inhibitors via pharmacophore modeling and QSAR analysis followed by in silico screening

Ahmed Mutanabbi Abdula, Reema Abu Khalaf, Mohammad S. Mubarak and Mutasem O. Taha [University of Jordan]

J. Comp. Chem. **32**, 463-482, 2011.

Glycosidases, including β -D-galactosidase, are involved in a variety of metabolic disorders, such as diabetes, viral or bacterial infections, and cancer. Accordingly, we were prompted to find new β -D-galactosidase inhibitors. Towards this end, we scanned the pharmacophoric space of this enzyme using a set of 41 known inhibitors. Genetic algorithm and multiple linear regression analyses were used to select an optimal combination of pharmacophoric models and physicochemical descriptors to yield self-consistent and predictive quantitative structure-activity relationship (QSAR).

2,4-Diamino-5-(2'-arylpropargyl)pyrimidine derivatives as new nonclassical antifolates for human dihydrofolate reductase inhibition

Oztekin Algul, Janet L. Paulsen, Amy C. Anderson [University of Connecticut]

J. Mol.Graph. and Mod., **29**, 608-613, 2011.

Dihydrofolate reductase (DHFR) has been a well-recognized target for the development of therapeutics for human cancers for several decades. Classical inhibitors of DHFR use an active transport mechanism to gain access to the cell; disabling this mechanism creates a pathway for resistance. In response, recent research focuses on nonclassical lipid-soluble DHFR inhibitors that are designed to passively diffuse through the membrane. Here, a new series of propargyl-linked antifolates are investigated as potential nonclassical human DHFR inhibitors.

Medicinal Chemistry and Drug Design (Cont'd)

Computational investigation of interactions between human H₂ receptor and its agonists

Xianqiang Sun, Yaozong Li, Weihua Li, Zhejun Xu, Yun Tang [East China University of Science and Technology]

J. Mol. Graph. and Mod., **29**, 693-701, 2011.

Type 2 histamine receptor (H₂R) is widely distributed in the body. Its main function is modulating the secretion of gastric acid. Most gastric acid-related diseases are closely associated with it. In this study, a combination of pharmacophore modeling, homology modeling, molecular docking and molecular dynamics methods were performed on human H₂R and its agonists to investigate interaction details between them. At first, a pharmacophore model of H₂R agonists was developed, which was then validated by QSAR and database searching.

Molecular modelling study on human histamine H1 receptor and its applications in virtual lead identification for designing novel inverse agonists

Sundarapandian Thangapandian [Gyeongsang National University (GNU)]; Shalini John; Sugunadevi Sakthiah; Keun Woo Lee

Molecular Simulation, **37**, 100 – 114, 2011.

Human histamine H1 receptor (HHR1) is one of the G protein-coupled receptors (GPCRs) known for their constitutive activation in the absence of agonist binding. Inverse agonists are the compounds that inhibit this constitutive activity of GPCRs. HHR1 is involved in allergic reactions and is also known to be constitutively active. An updated quantitative pharmacophore model, Hypo1, has been developed using a diverse set of known HHR1 inverse agonists employing the HypoGen algorithm as implemented in Accelrys Discovery Studio 2.1.

Quantitative Structure-Activity Relations

Molecular modeling studies on imidazo[4,5-b]pyridine derivatives as Aurora A kinase inhibitors using 3D-QSAR and docking approaches

Ping Lan, Wan-Na Chen, Wei-Min Chen [Jinan University]

European J. of Med. Chem., **46**, 77-94, 2011.

3D-QSAR and docking studies were performed on sixty imidazo[4,5-b]pyridine derivatives as Aurora A kinase inhibitors. The CoMFA and CoMSIA models using forty-eight molecules in the training set, gave r^2_{cv} values of 0.774 and 0.800, r^2 values of 0.975 and 0.977, respectively. The external validation indicated that both CoMFA and CoMSIA models possessed high predictive powers with r^2_{pred} values of 0.933 and 0.959, r^2_m values of 0.883 and 0.915, respectively.

Three-dimensional quantitative structure-selectivity relationships analysis guided rational design of a highly selective ligand for the cannabinoid receptor 2

Simone Brogi, Federico Corelli, Vincenzo Di Marzo, Alessia Ligresti, Claudia Mugnaini, Serena Pasquini, Andrea Tafi [Università degli Studi di Siena]

European J. of Med. Chem., **46**, 547-555, 2011.

3D-QSSR study for selectivity of a series of ligands for cannabinoid CB1 and CB2 receptors. 3D-QSSR exploration was expected to provide design information for drugs with high selectivity toward the CB2 receptor. The proposed 3D computational model was performed by Phase and generated taking into account a number of structurally diverse compounds characterized by a wide range of selectivity index values. The model proved to be predictive, with r^2 of 0.95 and Q^2 of 0.63. In order to get prospective experimental validation, the selectivity of an external data set of 39 compounds reported in the literature was predicted.

Quantitative Structure-Activity Relations (Cont'd)

Artificial neural network-based drug design for diabetes mellitus using flavonoids

Jagdish C. Patra [Nanyang Technological University] and Boon H. Chua

J. Comp. Chem. **32**, 555-567, 2011.

Diabetes mellitus is a chronic metabolic disease involving the failure to regulate glucose blood levels in the body and has been linked with numerous detrimental complications. Studies have shown that these complications can be linked to the activities of aldose reductase (AR), an enzyme of the polyol pathway. Flavonoids have been identified as good AR inhibitors (ARIs) and are also strong antioxidants with radical scavenging (RS) activity. We carried out quantitative structure-activity relationship analysis of flavones and flavonols (members of flavonoid family) using artificial neural networks.

3D-QSAR studies on caspase-mediated apoptosis activity of phenolic analogues

Yuanqiang Wang, Heng Zhang, Yong Lin, Qi Zhao and Hui Liu, Zhihua Lin [Chongqing University of Technology]

J. Mol.Mod., **17**, 1-8, 2011.

Phenols and its analogues are known to induce caspase-mediated apoptosis activity and cytotoxicity on various cancer cell lines. In the current work, two types of molecular field analysis techniques were used to perform the three dimension quantitative structure activity relationship (3D-QSAR) modeling between structural characters and anticancer activity of two sets of phenolic compounds, which are comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA).

Anthranilate derivatives as TACE inhibitors: Docking based CoMFA and CoMSIA analyses

Malkeet Singh Bahia, Shravan Kumar Gunda, Shwetha Reddy Gade, Saikh Mahmood and Ravikumar Muttineni, Om Silakari [Punjabi University]

J. Mol.Mod., **17**, 9-19, 2011.

Anthranilic acid based derivatives (ANTs) have been identified as a novel class of potent tumor necrosis factor- α converting enzyme (TACE) inhibitors. A computational strategy based on molecular docking studies, followed by CoMFA and CoMSIA analyses has been performed to elucidate the atomic details of the TACE/ANT interactions and also to identify the most important features impacting TACE inhibitory activity of ANTs.

3D QSAR pharmacophore model based on diverse IKK β inhibitors

Shanthi Nagarajan, Asif Ahmed, Hyunah Choo, Yong Seo Cho and Kwang-Seok Oh, Ae Nim Pae [Korea Institute of Science and Technology]

J. Mol.Mod., **17**, 209-218, 2011.

The inhibitor kappaB kinase β (IKK β) is a serine-threonine protein kinase that is critically involved in the activation of the transcription factor nuclear factor kappa B (NF- κ B) in response to various inflammatory stimuli. IKK β -selective inhibitors could prove useful for the treatment of inflammatory diseases. In the absence of structural information, a ligand-based approach can serve as an alternative to the virtual screening of large databases. We have developed a 3D QSAR pharmacophore model based on 23 IKK β inhibitors with $3 \text{ nM} \leq \text{IC}_{50} \leq 50000 \text{ nM}$.

Quantitative Structure-Activity Relations (Cont'd)

Molecular docking-based 3D-QSAR studies of pyrrolo[3,4-c]pyrazole derivatives as Aurora-A inhibitors

G. He [Sichuan University]; M. H. Qiu; R. Li; X. R. Song; X. Zheng; J. Y. Shi; G. B. Xu; J. Han; L. T. Yu; S. Y. Yang; L. J. Chen; Y. Q. Wei

Molecular Simulation, **37**, 31 – 42, 2011.

In recent years, Aurora kinases have been highlighted as attractive targets for the development of novel anti-cancer agents. To find the correlation between Aurora-A and its inhibitors, structure-based 3D-quantitative structure-activity relationship (QSAR) models were performed on a series of pyrrolo[3,4-c]pyrazole derivatives with comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) methods. Based on the docking results, predictive 3D-QSAR models were established, with cross-validated coefficient values (r^2_{cv}) up to 0.667 for CoMFA and 0.664 for CoMSIA, respectively.

A QSAR study for 2-(4-aminophenyl)benzothiazoles: using DFT optimisation of geometry of molecules

Rifaat Hilal [University of Cairo]; Shabaan A. K. Elroby

Molecular Simulation, **37**, 62 – 71, 2011.

Quantitative structure-activity relationships (QSARs) have been established for two sets of antitumour drugs 2-(4-aminophenyl)benzothiazoles (APBT). Constitutional, geometrical, topological, electronic descriptors (computed at the B3LYP/6-31G** level) and some empirical descriptors related to the hypophilicity were computed and analysed. Multiple regression analysis led to a set of equations that reflected the weight of each of the studied descriptors. The most relevant of these descriptors were grouped, and a new multiple regressions analysis was carried out and we arrived at the final QSAR models.

Carbon Nanoparticles

How do carbon nanotubes serve as carriers for gemcitabine transport in a drug delivery system?

Uthumporn Arsawang, Oraphan Saengsawang, Thanyada Rungrotmongkol, Purinchaya Sornmee, Kitiyaporn Wittayanarakul, Tawun Remsungnen, Supot Hannongbua [Chulalongkorn University]

J. Mol. Graph. and Mod., **29**, 591-596, 2011.

Aiming at understanding the molecular properties of the encapsulation of the anticancer drug gemcitabine in the single-walled carbon nanotube (SWCNT), molecular dynamics (MD) simulations were applied to the two scenarios; that of gemcitabine filling inside the SWCNT, and that of the drug in the free state. In excellent agreement with that yielded from the classical MD, the SMD energy profile confirms that the drug molecule prefers to locate inside the SWCNT.

Nanocatalyst structure as a template to define chirality of nascent single-walled carbon nanotubes

Diego A. Gómez-Gualdrón [Texas A&M University], Jin Zhao, and Perla B. Balbuena

Jou. Chem. Phys., **134**, 014705, 2011.

Chirality is a crucial factor in a single-walled carbon nanotube (SWCNT) because it determines its optical and electronic properties. A chiral angle spanning from 0° to 30° results from twisting of the graphene sheet conforming the nanotube wall and is equivalently expressed by chiral indexes (n,m). However, lack of chirality control during SWCNT synthesis is an obstacle for a widespread use of these materials. Here we use first-principles DFT and classical MD simulations to propose and illustrate basic concepts supporting that the nanocatalyst structure may act as a template to control the chirality during nanotube synthesis.

Carbon Nanotubes (Cont'd)

Multicomponent ballistic transport in narrow single wall carbon nanotubes: Analytic model and molecular dynamics simulations

T. Mutat [Technion, Haifa 32000], J. Adler, and M. Sheintuch

Jou. Chem. Phys., **134**, 044908, 2011.

The transport of gas mixtures through molecular-sieve membranes such as narrow nanotubes has many potential applications, but there remain open questions and a paucity of quantitative predictions. Our model, based on extensive molecular dynamics simulations, proposes that ballistic motion, hindered by counter diffusion, is the dominant mechanism. Our simulations of transport of mixtures of molecules between control volumes at both ends of nanotubes give quantitative support to the model's predictions.

Carbon doped boron phosphide nanotubes: A computational study

Mahmoud Mirzaei [Islamic Azad University]

J. Mol.Mod., **17**, 89-96, 2011.

A computational study based on density functional theory (DFT) calculations has been performed to investigate the properties of the electronic structure of carbon doped boron phosphide nanotube (C-doped BPNT). Pristine and the C-doped structures of two representative (6,0) zigzag and (4,4) armchair BPNTs have been investigated. At first, the geometries of the structures have been allowed to relax by optimization. Subsequently, NMR parameters have been calculated in the optimized structures.

Artificial neural network-based QSPR study on absorption maxima of organic dyes for dye-sensitised solar cells

Jie Xu [Wuhan Textile University]; Hui Zhang; Lei Wang; Guijie Liang; Luoxin Wang; Xiaolin Shen

Molecular Simulation, **37**, 1 – 10, 2011.

Analysis of ultrahigh frequency nanomechanical resonators, which are based on double-walled carbon nanotubes (DWCNTs) with various wall lengths, was carried out via classical molecular dynamics simulations. In the case of the inner wall entirely encapsulated inside the outer wall, the outer wall vibration has a significant effect on the vibration of the DWCNT; while in the case of the inner wall longer than the outer wall, the vibration of the extruded inner wall has a substantially stronger effect on the DWCNT vibration.

Translational dynamic friction analysis of double-walled carbon nanotubes

P. Liu [Institute of High Performance Computing, Singapore]; Y. W. Zhang

Molecular Simulation, **37**, 84 – 89, 2011.

Conflicting results on the effects of commensurability, overlap area, helicity and end configuration of double-walled carbon nanotubes (DWCNTs) on translational intertube friction have been reported. We perform molecular dynamics simulations on DWCNTs with different commensurabilities, overlap areas, helicities and end configurations to analyse the intertube friction behaviour and clarify these results.

Crystal Growth

Crystal growth investigations of ice/water interfaces from molecular dynamics simulations: Profile functions and average properties

M. S. Gulam Razul [Saint Francis Xavier University] and P. G. Kusalik

Jou. Chem. Phys., **134**, 014710, 2011.

Attempts to simulate crystal growth of ice from liquid water and to provide a consistent microscopic description of this process have been challenging tasks. In this paper we have adapted our previously developed molecular dynamics simulation methodology to enable the investigation of steady-state directional crystal growth/melting of ice. Specifically, we examine ice/water systems of the (001), (110), and (111) faces of ice Ic and the (0001), (10 $\bar{1}$ 0), and (11 $\bar{2}$ 0) faces of ice Ih, where the TIP4P, TIP4P-Ew, and SPC/E water models have been utilized.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Nanomaterials in biological environment: a review of computer modelling studies

A. J. Makarucha, N. Todorova and I. Yarovsky [RMIT University]

Europ. Biophys. Jou., **40**, 103-115, 2011.

Nanotechnology is set to impact a vast range of fields, including computer science, materials technology, engineering/manufacturing and medicine. As nanotechnology grows so does exposure to nanostructured materials, thus investigation of the effects of nanomaterials on biological systems is paramount. Computational techniques can allow investigation of these systems at the nanoscale, providing insight into otherwise unexaminable properties, related to both the intentional and unintentional effects of nanomaterials.

A partial-propensity formulation of the stochastic simulation algorithm for chemical reaction networks with delays

Rajesh Ramaswamy [Swiss Institute of Bioinformatics] and Ivo F. Sbalzarini

Jou. Chem. Phys., **134**, 014106, 2011.

Several real-world systems, such as gene expression networks in biological cells, contain coupled chemical reactions with a time delay between reaction initiation and completion. The non-Markovian kinetics of such reaction networks can be exactly simulated using the delay stochastic simulation algorithm (dSSA). The computational cost of dSSA scales with the total number of reactions in the network. We reduce this cost to scale at most with the smaller number of species by using the concept of partial reaction propensities.

Protein Secondary Structure

Conformational Analysis of a Nitroxide Side Chain in an α -Helix with Density Functional Theory

Dora Toledo Warshaviak, Laura Serbulea, K. N. Houk [UCLA School of Medicine], and Wayne L. Hubbell

J. Phys. Chem. B., **115**, 397–405, 2011.

In site directed spin labeling, a nitroxide side chain is introduced at a selected site in a protein; the most commonly used is a disulfide-linked side chain designated R1. To identify the intraresidue interactions that stabilize particular rotamers of R1 in the absence of interactions with nearby side chains in a helix, and to evaluate models for the internal motion of the side chain, quantum mechanical calculations were performed on a relevant fragment of R1 in a 10-residue α -helix.

Comparative or Homology Modeling

The Possible Structural Models for Polyglutamine Aggregation: A Molecular Dynamics Simulations Study

Zheng-Li Zhou, Jian-Hua Zhao, Hsuan-Liang Liu [National Taipei University of Technology], Josephine W. Wu, Kung-Tien Liu, Chih-Kuang Chuang, Wei-Bor Tsai, Yih Ho

J. Biomol. Stru. and Dyn., **28**, 743-758, 2011.

Huntington's disease is a neurodegenerative disorder caused by a polyglutamine (polyQ) expansion near the N-terminus of huntingtin. Previous studies have suggested that polyQ aggregation occurs only when the number of glutamine (Q) residues is more than 36-40, the disease threshold. In this study, we designed 18 simulation trials to determine the possible structural models for polyQ nucleation and aggregation with various shapes and sizes of initial β -helical structures, such as left-handed circular, right-handed rectangular, and left- and right-handed triangular.

PDZ Binding to the BAR Domain of PICK1 is Elucidated by Coarse-grained Molecular Dynamics

Yi He, Adam Liwo, Harel Weinstein, Harold A. Scheraga [Cornell University]

J. Molec. Bio. **405**, 298-314, 2011.

A key regulator of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor traffic, PICK1 is known to interact with over 40 other proteins, including receptors, transporters and ionic channels, and to be active mostly as a homodimer. Here, we identify interactions between the component PDZ and BAR domains of PICK1 by calculating possible binding sites for the PDZ domain of PICK1 (PICK1-PDZ) to the homology-modeled, crescent-shaped dimer of the PICK1-BAR domain using multiplexed replica-exchange molecular dynamics (MREMD) and canonical molecular dynamics simulations with the coarse-grained UNRES force field.

Homology Model of the Na^+ /Proline Transporter PutP of *Escherichia coli* and Its Functional Implications

Elena Olkhova, Michael Raba, Susanne Bracher, Daniel Hilger, Heinrich Jung [Biozentrum der LMU München]

J. Molec. Bio. **406**, 59-74, 2011.

Na^+ /solute symporters are essential membrane integrated proteins that couple the flow of Na^+ ions driven by electrochemical Na^+ gradients to the transport of solutes across biological membranes. Here, we used a combination of molecular modeling techniques and evolutionary conservation analysis to construct and validate a first model of the Na^+ /proline symporter PutP of *Escherichia coli* based on the crystal structure of the bacterial Na^+ /galactose symporter vSGLT.

Comparative or Homology Modeling (Cont'd)

Protein modeling and active site binding mode interactions of myrosinase–sinigrin in *Brassica juncea*—An in silico approach

Rajender Kumar [CCSHAU, Hisar], Sandeep Kumar, Seema Sangwan, Inderjit Singh Yadav, Rakesh Yadav

J. Mol. Graph. and Mod., **29**, 740-746, 2011.

Myrosinase, the only known S-glycosidase, occurs particularly in Cruciferae family. It is responsible for the hydrolysis of glucosinolates and serves as a vital element of plant defense system. Homolog templates from *S. alba* exhibited 72% identity with target sequence. The model was optimized by using molecular dynamics (MD) approach together with simulated annealing (SA) methods in the same Modeller program, and eventually verified and validated on SAVES (Structure Analysis and Verification Server) and PROCHECK programs, respectively.

Studies of tricyclic piperazine/piperidine furnished molecules as novel integrin $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ dual antagonists using 3D-QSAR and molecular docking

Yulian Yan, Yan Li [Dalian University of Technology], Shuwei Zhang, Chunzhi Ai

J. Mol. Graph. and Mod., **29**, 747-762, 2011.

The development of injectable integrin $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ dual antagonists attracts much attention of research for treating of acute ischemic diseases in recent years. In this work, based on a dataset composed of 102 tricyclic piperazine/piperidine furnished dual $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ antagonists, a variety of in silico modeling approaches including the comparative molecular field analysis (CoMFA), comparative similarity indices analysis (CoMSIA), and molecular docking were applied to reveal the requisite 3D structural features impacting the biological activities.

A leucine-rich repeat assembly approach for homology modeling of the human TLR5-10 and mouse TLR11-13 ectodomains

Tiandi Wei, Jing Gong [Ludwig-Maximilians-Universität München], Shaila C. Rössle, Ferdinand Jamitzky and Wolfgang M. Heckl, et al.

J. Mol. Mod., **17**, 27-36, 2011.

So far, 13 groups of mammalian Toll-like receptors (TLRs) have been identified. Most TLRs have been shown to recognize pathogen-associated molecular patterns from a wide range of invading agents and initiate both innate and adaptive immune responses. However, the quality of the predicted models that are generated from full-length templates can be limited due to low sequence identity between the target and templates. To obtain better templates for modeling, we have developed an LRR template assembly approach.

Homology modeling, molecular dynamic simulation and docking studies of cyclin dependent kinase 1

Lei Zhang, Huawei Zhu, Qiang Wang, Hao Fang and Wenfang Xu, Minyong Li. [Shandong University]

J. Mol. Mod., **17**, 219-226, 2011.

In order to develop promising cyclin dependent kinase 1 inhibitors, homology modeling, docking and molecular dynamic simulation techniques were applied to get insight into the functional and structural properties of cyclin dependent kinase 1 (CDK1). Since there is no reported CDK1 crystal structural data, the three dimensional structure of CDK1 was constructed based on homology modeling. An extensive dynamic simulation was also performed on a Flavopiridol-CDK1 complex for probing the binding pattern of Flavopiridol in the active site of CDK1.

Comparative or Homology Modeling (Cont'd)

Molecular modeling studies of Fatty acyl-CoA synthetase (FadD13) from *Mycobacterium tuberculosis*—a potential target for the development of antitubercular drugs

Nidhi Jatana, Sarvesh Jangid, Garima Khare, Anil K. Tyagi and Narayanan Latha [Sri Venkateswara College, New Delhi]

J. Mol.Mod., **17**, 301-313, 2011.

Biochemical studies on Fatty Acyl-CoA Synthetases (FadD13), one of the gene products of *mymA* operon, have provided insights into the involvement of this protein in the activation of fatty acids. Due to non-availability of the crystal structure of FadD13, we have employed in silico approaches to resolve and characterize the structure of this important protein of *M. tb*. A three dimensional model of *M. tb* FadD13 was predicted by a de novo structure prediction server that integrates fragment assembly with SimFold energy function. With the aid of molecular mechanics and dynamics methods, the final model was obtained and assessed subsequently for global and local accuracy by various assessment programs.

The binding modes and binding affinities of artemisinin derivatives with *Plasmodium falciparum* Ca²⁺-ATPase (PfATP6)

Pradeep Kumar Naik [Jaypee University of Information Technology], Mani Srivastava, Prasad Bajaj, Sankalp Jain and Abhishek Dubey, et al.

J. Mol.Mod., **17**, 333-357, 2011.

Noncompetitive inhibitors of sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) orthologue (PfATP6) of *P. falciparum* have important therapeutic value in the treatment of malaria. Artemisinin and its analogues are one such class of inhibitors which bind to a hydrophobic pocket located in the transmembrane region of PfATP6 near the biomembrane surface and interfere with calcium transport. The 3D structure of PfATP6 was modeled by homology modeling. A library consisting of 150 artemisinin analogues has been designed. Their molecular interactions and binding affinities with modeled PfATP6 protein have been studied using the docking, molecular mechanics based on generalized Born/surface area (MM-GBSA) solvation model and multi-ligand bimolecular association with energetics (eMBrAcE).

Protein Confirmational Analysis

A Statistical Analysis of the PPII Propensity of Amino Acid Guests in Proline-Rich Peptides

Mahmoud Moradi, Volodymyr Babin, Celeste Sagui, Christopher Roland [North Carolina State University]

Biophysical Journal. **100**, 1083-1093, 2011.

There has been considerable debate about the intrinsic PPII propensity of amino-acid residues in denatured polypeptides. Experimentally, the propensity scale is based on the behavior of guest amino-acid residues placed in the middle of polyproline hosts. We have used classical molecular dynamics simulations, with state-of-the-art force fields to carry out a comprehensive analysis of the conformational equilibria of the proline-based host oligopeptides with single guests.

Protein Conformational Analysis (Cont'd)

Conformational Properties of Methyl β -Maltoside and Methyl α - and β -Cellobioside Disaccharides

Elizabeth Hatcher, Elin Sawen, Goran Widmalm, and Alexander D. MacKerell, Jr. [University of Maryland]

J. Phys. Chem. B., **115**, 597–608, 2011.

An investigation of the conformational properties of methyl β -maltoside, methyl α -cellobioside, and methyl β -cellobioside disaccharides using NMR spectroscopy and molecular dynamics (MD) techniques, is presented. Emphasis is placed on validation of a recently presented force field for hexopyranose disaccharides followed by elucidation of the conformational properties of two different types of glycosidic linkages, α -(1 $\rightarrow$ 4) and β -(1 $\rightarrow$ 4). Both gas-phase and aqueous-phase simulations are performed to gain insight into the effect of solvent on the conformational properties.

Protein Dynamics

Thermal Stability and Unfolding Pathways of Sso7d and its Mutant F31A: Insight from Molecular Dynamics Simulation

Xianjin Xu, Jiguo Su, Weizu Chen, Cunxin Wang [Beijing University of Technology]

J. Biomol. Stru. and Dyn., **28**, 717-727, 2011.

The thermo-stability and unfolding behaviors of a small hyperthermophilic protein Sso7d as well as its single-point mutation F31A are studied by molecular dynamics simulation at temperatures of 300 K, 371 K and 500 K. Simulations at 300 K show that the F31A mutant displays a much larger flexibility than the wild type, which implies that the mutation obviously decreases the protein's stability. In the simulations at 371 K, although larger fluctuations were observed, both of these two maintain their stable conformations.

Effect of ligand binding on the intraminimum dynamics of proteins

Burak Alakent [Bogazici University], Sena Baskan and Pemra Doruker

J. Comp. Chem. **32**, 483–496, 2011.

Effects of ligand binding on protein dynamics are studied via molecular dynamics (MD) simulations on two different enzymes, dihydrofolate reductase (DHFR) and triosephosphate isomerase (TIM), in their unliganded (free) and liganded states. Domain motions in MD trajectories are analyzed by collectivities and rotation angles along the principal components (PCs). We suggest that stochastic time series modeling is a promising method to be used in determining subtle perturbations in protein dynamics.

Computational Protein Design Using Flexible Backbone Remodeling and Resurfacing: Case Studies in Structure-Based Antigen Design

Bruno E. Correia, Yih-En Andrew Ban, Della J. Friend, Katharine Ellingson, Hengyu Xu, Erica Boni, Tyler Bradley-Hewitt, Jessica F. Bruhn-Johannsen, Leonidas Stamatatos, Roland K. Strong, William R. Schief [University of Washington]

J. Molec. Bio. **405**, 284-297, 2011.

Computational protein design has promise for vaccine design and other applications. We previously transplanted the HIV 4E10 epitope onto non-HIV protein scaffolds for structural stabilization and immune presentation. Here, we developed two methods to optimize the structure of an antigen, flexible backbone remodeling and resurfacing, and we applied these methods to a 4E10 scaffold. These results indicate that flexible-backbone remodeling and resurfacing are useful tools for antigen optimization and protein engineering generally.

Protein Dynamics (Cont'd)

Atomic-Level Characterization of the Ensemble of the A β (1–42) Monomer in Water Using Unbiased Molecular Dynamics Simulations and Spectral Algorithms

Nikolaos G. Sgourakis, Myrna Merced-Serrano, Christos Boutsidis, Petros Drineas, Zheming Du, Chunyu Wang, Angel E. Garcia [Rensselaer Polytechnic Institute]

J. Molec. Bio. **405**, 570-583, 2011.

A β (1–42) is the highly pathologic isoform of amyloid- β , the peptide constituent of fibrils and neurotoxic oligomers involved in Alzheimer's disease. Recent studies on the structural features of A β in water have suggested that the system can be described as an ensemble of distinct conformational species in fast exchange. Here, we use replica exchange molecular dynamics (REMD) simulations to characterize the conformations accessible to A β 42 in explicit water solvent, under the ff99SB force field.

A Structural Model for Apolipoprotein C-II Amyloid Fibrils: Experimental Characterization and Molecular Dynamics Simulations

Chai Lean Teoh [University of Melbourne, Parkville], Chi L.L. Pham, Nevena Todorova, Andrew Hung, Craig N. Lincoln, Emma Lees, Yuen Han Lam, Katrina J. Binger, Neil H. Thomson, Sheena E. Radford, Trevor A. Smith, Shirley A. Müller, Andreas Engel, Michael D.W. Griffin, Irene Yarovsky, Paul R. Gooley, Geoffrey J. Howlett

J. Molec. Bio. **405**, 1246-1266, 2011.

The self-assembly of specific proteins to form insoluble amyloid fibrils is a characteristic feature of a number of age-related and debilitating diseases. Lipid-free human apolipoprotein C-II (apoC-II) forms characteristic amyloid fibrils and is one of several apolipoproteins that accumulate in amyloid deposits located within atherosclerotic plaques. Fully solvated all-atom molecular dynamics (MD) simulations showed that the model contained a stable cross- β -core with a flexible connecting loop devoid of persistent secondary structure. The time course of the MD simulations revealed that charge clusters in the fibril rearrange to minimize the effects of same-charge interactions inherent in parallel in-register models.

Spontaneous Proton Transfer to a Conserved Intein Residue Determines On-Pathway Protein Splicing

Brian Pereira, Philip T. Shemella, Gil Amitai, Georges Belfort, Saroj K. Nayak, Marlene Belfort [Wadsworth Center, New York State Department of Health]

J. Molec. Bio. **405**, 43-48, 2011.

The discovery of inteins, which are protein-splicing elements, has stimulated interest for various applications in chemical biology, bioseparations, drug delivery, and sensor development. In this study, we demonstrate that formation of a previously identified branched intermediate is the critical step for determining splicing over cleavage products. By combining experimental assays and quantum mechanical simulations, we identify the electrostatic interactions that are important to the dynamics of the reaction steps.

Differences in active-site microarchitecture explain the dissimilar behaviors of PBP5 and 6 in *Escherichia coli*

Chiranjit Chowdhury, Anindya S. Ghosh [Indian Institute of Technology, Kharagpur]

J. Mol. Graph. and Mod., **29**, 650-656, 2011.

Out of the four DD-carboxypeptidases (DD-CPases) in *Escherichia coli*, only penicillin-binding protein (PBP) 5 performs physiological functions such as maintaining cell shape; its nearest homolog, PBP6, cannot perform such functions. The recently solved crystal structure of PBP6 cannot explain the reason for the observed functional discrepancies between the two proteins. To determine why the activities of these enzymes differ, we used molecular modeling, and docking analyses with substrate-mimetic ligands to estimate how amino-acid alterations in the morphology maintenance domain would affect the structure of PBP and hence its substrate specificity.

Protein Dynamics (Cont'd)

Analysis of the stabilities of hexameric amyloid- β (1–42) models using discrete molecular dynamics simulations

Sijung Yun, Sajung Yun, H. Robert Guy [National Institutes of Health, 37 Convent Drive, Bethesda]

J. Mol. Graph. and Mod., **29**, 657-662, 2011.

Amyloid- β (A β) oligomers appear to play a pivotal role in Alzheimer's disease. A 42 residue long alloform, A β 42, is closely related to etiology of the disease. In vitro results show evidences of hexamers; however structures of these hexamers have not been resolved experimentally. Here, we use discrete molecular dynamics (DMD) to analyze long duration stabilities of A β 42 hexamer models developed previously in our lab. A model of an annular protofibril composed of 36 A β peptides was also simulated.

Effects of osmolytes on the helical conformation of model peptide: Molecular dynamics simulation

Faramarz Mehrnejad [Azarbaijan University of Tarbiat Moallem], Mohammad Mehdi Ghahremanpour, Mahmoud Khadem-Maaref, and Farahnoosh Doustdar

Jou. Chem. Phys., **134**, 035104, 2011.

Co-solvents such as glycerol and sorbitol are small organic molecules solvated in the cellular solutions that can have profound effects on the protein structures. Here, the molecular dynamics simulations and comparative structural analysis of magainin, as a peptide model, in pure water, 2,2,2-trifluoroethanol/water, glycerol/water, and sorbitol/water are reported. Our results show that the peptide NMR structure is largely maintained its native structure in osmolytes–water mixtures.

Structure and dynamics of human vimentin intermediate filament dimer and tetramer in explicit and implicit solvent models

Zhao Qin and Markus J. Buehler [Massachusetts Institute of Technology]

J. Mol. Mod., **17**, 37-48, 2011.

Intermediate filaments, in addition to microtubules and microfilaments, are one of the three major components of the cytoskeleton in eukaryotic cells, and play an important role in mechanotransduction as well as in providing mechanical stability to cells at large stretch. Here we present extensive simulations and structural analyses of the model based on ultra large-scale atomistic-level simulations in an explicit solvent model, with system sizes exceeding 500,000 atoms and simulations carried out at 20 ns time-scales.

Atomistic modeling of apatite-collagen composites from molecular dynamics simulations extended to hyperspace

Patrick Duchstein and Dirk Zahn [Max-Planck-Institut für Chemische Physik fester Stoffe]

J. Mol. Mod., **17**, 73-79, 2011.

The preparation of atomistic models of apatite-collagen composite mimicking enamel at length scales in the range of 1–10 nanometers is outlined. This bio-composite is characterized by a peculiar interplay of the collagen triplehelix and the apatite crystal structure. Structural coherence is however only obtained after drastic rearrangements, namely the depletion of protein-protein hydrogen bonds and the incorporation of calcium triangles which are stabilized by salt-bridges with the collagen molecule.

Protein Dynamics (Cont'd)

Local and Bulk Hydration of Zwitterionic Glycine and its Analogues through Molecular Simulations

Andrew White and Shaoyi Jiang [University of Washington, Seattle]

J. Phys. Chem. B., **115**, 660–667, 2011.

Molecular dynamics simulations were used to characterize the differences in hydration between glycine and two of its zwitterionic analogues: N,N-dimethylglycine and N,N,N-trimethylglycine (glycine betaine). The hydration of dodecane and oligo(ethylene glycol) was studied for reference. Both structuring and dynamics of bulk and bound water were examined using a variety of properties and at multiple concentrations. Metrics, such as radial distribution functions and residence times, were used to characterize hydration.

Simulation of the Amide I Absorption of Stacked β -Sheets

Eeva-Liisa Karjalainen, Harish Kumar Ravi, and Andreas Barth [Stockholm University]

J. Phys. Chem. B., **115**, 749–757, 2011.

In this work, the infrared (IR) amide I spectral characteristics of stacked β -sheets were modeled using the transition dipole coupling model. For a test set of β -sheet stacks, the simulated amide I spectrum was analyzed with respect to the following parameters; intersheet distance, relative rotation of the sheets with respect to each other and the effect of number of sheets stacked. The amide I maximum shifts about 5 cm^{-1} to higher wavenumbers when the intersheet distance between two identical β -sheets decreases from 20 to 5 Å.

Exploring the Intermediate States of ADP–ATP Exchange: A Simulation Study on Eg5

Wei Zhang [Southern Research Institute, Birmingham]

J. Phys. Chem. B., **115**, 784–795, 2011.

While mitotic kinesins have attracted significant attention in recent years as new anticancer drug targets, the underlying mechanism of kinesin-catalyzed ATP hydrolysis is still under investigation. Crystal structures of Eg5, one of the best-studied kinesins, have been solved in both ADP-bound and ATP-bound states. Systematic molecular dynamics simulations were performed in this study to mimic different nucleotide binding states and explore the critical structural and dynamic variations during ADP–ATP exchange.

Conformational Analysis of Aqueous BMP-2 Using Atomistic Molecular Dynamics Simulations

Augusto F. Oliveira [Technische Universitat Dresden], Sibylle Gemming, and Gotthard Seifert

J. Phys. Chem. B., **115**, 1122–1130, 2011.

BMP-2 is an osteoinductive protein, involved in the differentiation and proliferation of osteoblasts, with potential application as bioactive agent in bone implants and scaffolds. Since the three-dimensional structure of a protein usually determines its bioactivity, in order to efficiently design bone implants activated with BMP-2 it is essential to identify the factors influencing the protein conformation. In the present work, atomistic molecular dynamics simulations are employed to investigate the BMP-2 monomer and homodimer in vacuum and water.

Protein Dynamics (Cont'd)

Steered Molecular Dynamics Simulations of the Electron Transfer Complex between Azurin and Cytochrome c_{551}

Anna Rita Bizzarri [Universita della Tuscia]

J. Phys. Chem. B., **115**, 1211–1219, 2011.

The unbinding properties of the transient complex between the electron transfer proteins azurin and cytochrome c_{551} have been investigated by steered molecular dynamics simulations by pulling four different atoms of cytochrome c_{551} . The atoms to be pulled have been chosen to closely match the conditions of a previous experimental study by atomic force spectroscopy. The temporal evolution of the distance between different couples of atoms of the intermolecular hydrogen bonds and of the unbinding force have been analyzed for the various setups and by applying seven different pulling speed values.

Effects of G33A and G33I Mutations on the Structures of Monomer and Dimer of the Amyloid- β Fragment 29–42 by Replica Exchange Molecular Dynamics Simulations

Yan Lu, Guanghong Wei [Fudan University], and Philippe Derreumaux

J. Phys. Chem. B., **115**, 1282–1288, 2011.

The early formed oligomers of amyloid- β proteins with 40 and 42 amino acids are believed to be the culprits of Alzheimer's disease. A β 1–42 peptides with alanine and isoleucine mutations of glycine 33 are known to be much less toxic than the wild-type A β 1–42 and promote the aggregation process in vitro. As a first step toward understanding the impact of G33A and G33I mutations on the earliest steps along the A β 1–42 aggregation pathway, we have studied the structures of the monomer and dimer of A β 29–42 and its two G33 variants using coarse-grained replica exchange molecular dynamics simulations.

Modelling and predicting the binding mechanics of HIV P1053-0.5 β antibody complex

Yeng-Tseng Wang [National Center for High-Performance Computing, Hsinchu]; Zhi-Yuan Su

Molecular Simulation, **37**, 164 – 171, 2011.

Simulating antigen-antibody interactions is crucial in understanding the mechanics of antigen-antibody binding in medical science. In this study, molecular dynamics simulations are performed to analyse the dissociation of the P1053-0.5 β antibody complex structure. The two-dimensional free energy profiles of the complex structure are extracted using the weighted histogram analysis method, and the binding pathway is then predicted using a modified form of the MaxFlux-PRM method.

Behavior of the ATP grasp domain of biotin carboxylase monomers and dimers studied using molecular dynamics simulations

Brian R. Novak, Dorel Moldovan, Grover L. Waldrop and Marcio S. de Queiroz [Louisiana State University]

Proteins: Stru. Fun. and Bioinfo. **79**, 622–632, 2011.

The enzyme biotin carboxylase (BC) uses adenosine triphosphate (ATP) to carboxylate biotin and is involved in fatty acid synthesis. Structural evidence suggests that the B domain of BC undergoes a large hinge motion of $\sim 45^\circ$ when binding and releasing substrates. Using molecular dynamics simulations, we evaluate the free energy profile along a closure angle of the B domain of *E. coli* BC for three cases: a monomer without bound Mg_2ATP , a monomer with bound Mg_2ATP , and a homodimer with bound Mg_2ATP in one subunit.

Protein Dynamics (Cont'd)

Molecular dynamics simulation of β_2 -microglobulin in denaturing and stabilizing conditions

Federico Fogolari [Universita' di Udine], Alessandra Corazza, Nicola Varini, Matteo Rotter, Devrim Gumral, Luca Codutti, Enrico Rennella, Paolo Viglino, Vittorio Bellotti and Gennaro Esposito

Proteins: Stru. Fun. and Bioinfo. **79**, 417–427, 2011.

β_2 -Microglobulin has been a model system for the study of fibril formation for 20 years. we use molecular dynamics to address three key aspects of β_2 -microglobulin, which are known to be relevant to amyloid formation: (1) 60 ns molecular dynamics simulations of β_2 -microglobulin in trifluoroethanol and in conditions mimicking low pH are used to study the behavior of the protein in environmental conditions that are able to trigger amyloid formation; (2) adaptive biasing force molecular dynamics simulation is used to force cis-trans isomerization at Proline 32. (3) molecular dynamics simulation of highly concentrated doxycycline in the presence of β_2 -microglobulin provides details of the binding modes of the drug and a rationale for its effect.

Free Energy Calculations

The severity of osteogenesis imperfecta: A comparison to the relative free energy differences of collagen model peptides

Kyung-Hoon Lee, Krzysztof Kuczera and Mark M. Banaszak Holl [University of Michigan]

Biopolymers. **95**, 182–193, 2011.

Molecular dynamics simulations were carried out to calculate free energy differences between the folded and unfolded states of wild type and mutant collagen model peptides. The calculated stability of the collagen models was compared with the severity of osteogenesis imperfecta. Free energy differences of Gly $\rightarrow$ Xaa (Xaa: Ser, Cys, Glu, and Asp) mutations between the wild type and the mutants at position 15 of the model peptide were 3.8, 4.2, 5.6, and 8.8 kcal/mol, respectively.

Free energy calculation using molecular dynamics simulation combined with the three-dimensional reference interaction site model theory. II. Thermodynamic integration along a spatial reaction coordinate

Tatsuhiko Miyata [Institute for Molecular Science, 38 Nishigo-Naka], Yasuhiro Ikuta, and Fumio Hirata

Jou. Chem. Phys., **134**, 044127, 2011.

We propose the thermodynamic integration along a spatial reaction coordinate using the molecular dynamics simulation combined with the three-dimensional reference interaction site model theory. This method provides a free energy calculation in solution along the reaction coordinate defined by the Cartesian coordinates of the solute atoms. The proposed method is based on the blue moon algorithm which can, in principle, handle any reaction coordinate as far as it is defined by the solute atom positions.

Escorted free energy simulations

Suriyanarayanan Vaikuntanathan [University of Maryland] and Christopher Jarzynski

Jou. Chem. Phys., **134**, 054107, 2011.

We describe a strategy to improve the efficiency of free energy estimates by reducing dissipation in nonequilibrium Monte Carlo simulations. This strategy generalizes the targeted free energy perturbation approach [C. Jarzynski, *Phys. Rev. E* **65**, 046122 (2002)] to nonequilibrium switching simulations, and involves generating artificial, “escorted” trajectories by coupling the evolution of the system to updates in external work parameter.

Free Energy Calculations (Cont'd)

Docking study and binding free energy calculation of poly (ADP-ribose) polymerase inhibitors

Kazuki Ohno, Takashi Mitsui, Yoshiaki Tanida, Azuma Matsuura and Hideaki Fujitani, Masaya Orita, [Astellas Pharma Inc.] et al.

J. Mol.Mod., **17**, 383-389, 2011.

Recently, the massively parallel computation of absolute binding free energy with a well-equilibrated system (MP-CAFEE) has been developed. The present study aimed to determine whether the MP-CAFEE method is useful for drug discovery research. In the drug discovery process, it is important for computational chemists to predict the binding affinity accurately without detailed structural information for protein / ligand complex. We investigated the absolute binding free energies for Poly (ADP-ribose) polymerase-1 (PARP-1) / inhibitor complexes, using the MP-CAFEE method.

New Method for Calculating the Absolute Free Energy of Binding: The Effect of a Mobile Loop on the Avidin/Biotin Complex

Ignacio J. General, Ralitsa Dragomirova, and Hagai Meirovitch [University of Pittsburgh School of Medicine]

J. Phys. Chem. B., **115**, 168–175, 2011.

Hypothetical scanning molecular dynamics (HSMD) is a relatively new method for calculating the absolute free energy and entropy. HSMD is extended here for the first time for calculating the absolute free energy of binding, ΔA^0 , as applied to the avidin–biotin complex. With HSMD the ligand is built (more accurately reconstructed) from nothing in solvent and in the protein, in contrast to the commonly used methods where the ligand is annihilated (by thermodynamic integration) in these environments.

Accounting for conformational entropy in predicting binding free energies of protein-protein interactions

Hetunandan Kamisetty, Arvind Ramanathan, Chris Bailey-Kellogg and Christopher James Langmead [Carnegie Mellon University]

Proteins: Stru. Fun. and Bioinfo. **79**, 444–462, 2011.

Protein-protein interactions are governed by the change in free energy upon binding, $\Delta G = \Delta H - T\Delta S$. These interactions are often marginally stable, so one must examine the balance between the change in enthalpy, ΔH , and the change in entropy, ΔS , when investigating known complexes, characterizing the effects of mutations, or designing optimized variants. To perform a large-scale study into the contribution of conformational entropy to binding free energy, we developed a technique called GOBLIN (Graphical mOdel for BiomoLecular Interactions) that performs physics-based free energy calculations for protein-protein complexes under both side-chain and backbone flexibility.

Ligand Binding/Docking

Characterizing the Energetic States of the GluR2 Ligand Binding Domain Core-Dimer

Michael Yonkunas, Maria Kurnikova [Carnegie Mellon University]

Biophysical Journal. **100**, L5-L7, 2011.

Tetrameric ligand binding domains of the family of ionotropic glutamate receptors assemble as dimers-of-dimers. Crystallographic studies of several glutamate receptor subtype isolated core-dimers suggest a single stable dimeric conformation. Molecular dynamics simulations and continuum electrostatics calculations reveal that the active glutamate bound form of the ligand-binding domain found in typical crystal structures is the preferred energetic state of the isolated core-dimer in the presence of agonist glutamate.

Ligand Binding/Docking (Cont'd)

All-Atom Molecular Dynamics Simulations Reveal Significant Differences in Interaction between Antimycin and Conserved Amino Acid Residues in Bovine and Bacterial bc₁ Complexes

Oleksandr Kokhan, Vladimir P. Shinkarev [University of Illinois at Urbana-Champaign]

Biophysical Journal. **100**, 720-728, 2011.

Antimycin A is the most frequently used specific and powerful inhibitor of the mitochondrial respiratory chain. We used all-atom molecular dynamics (MD) simulations to study the dynamic aspects of the interaction of antimycin A with the Q_i site of the bacterial and bovine bc₁ complexes embedded in a membrane. The MD simulations revealed considerable conformational flexibility of antimycin and significant mobility of antimycin, as a whole, inside the Q_i pocket.

A QSAR study using MTD method and Dragon descriptors for a series of selective ligands of α_2 C adrenoceptor

Ana Borota, Maria Mracec [Institute of Chemistry Timisoara of the Romanian Academy], Alexandra Gruia, Ramona Rad-Curpăn, Liliana Ostopovici-Halip, Mircea Mracec

European J. of Med. Chem., **46**, 877-884, 2011.

A QSAR analysis of the binding affinities for a series of 43 quinoline derivatives active against the α_2 C adrenergic receptor was performed. Multiple linear regressions (MLR) were obtained using the minimum topological difference (MTD) descriptor and various descriptors which were calculated with Dragon3.0. The variable selection was performed either through the forward stepwise method or backward stepwise combined with forward stepwise methods, providing two satisfactory models.

Protein-based alignment in 3D-QSAR of FBPase inhibitors

Ping Yi, Ying-Tong Di, Wei Liu, Xiao-Jiang Hao [Honghe University], Yong Ming, Du-Shu Huang, Jin Yang, Zhong-Zhou Yi, Zi-Jing Li, Rui-Dong Yang, Ju-Cheng Zhang

European J. of Med. Chem., **46**, 885-892, 2011.

Three-dimensional quantitative structure-activity relationship (3D-QSAR) studies were performed on Fructose-1, 6-bisphosphatase (FBPase) inhibitors, based on molecular docking obtained by using GOLD and comparative molecular field analysis (CoMFA). Three random splits into training and test sets had been performed and the high leave-one-out (LOO) cross-validated correlation coefficients q^2 of 0.781, 0.725 and 0.801, respectively, revealed that the models are useful tools for the prediction of test sets as well as newly designed structures against FBPase activity.

Steered molecular dynamics simulations of ligand-receptor interaction in lipocalins

Janne Kalikka and Jaakko Akola [University of Jyväskylä]

Europ. Biophys. Jou., **40**, 181-194, 2011.

Retinol binding protein (RBP) and an engineered lipocalin, DigA16, have been studied using molecular dynamics simulations. Special emphasis has been placed on explaining the ligand-receptor interaction in RBP-retinol and DigA16-digoxigenin complexes, and steered molecular dynamics simulations of 10–20 ns have been carried out for the ligand expulsion process. The ligand binding energies have been estimated based on the linear response approximation of binding affinity by using a previous parametrization for retinoids and RBP.

Ligand Binding/Docking (Cont'd)

Screening from the World's Largest TCM Database Against H1N1 Virus

Tung-Ti Chang, Mao-Feng Sun, Hsin-Yi Chen, Fuu-Jen Tsai, Mark Fisher, Jaung-Geng Lin, Calvin Yu-Chian Chen [China Medical University]

J. Biomol. Stru. and Dyn., **28**, 773-786, 2011.

Recently, oseltamivir (Tamiflu) resistant influenza viruses are identified; which further emphasizes the urgency in developing new antiviral agents. In influenza virus replication cycle, viral surface glycoprotein, hemagglutinin, is responsible for viral entry into host cells. To develop novel antiviral agent that inhibits viral entry, we analyzed 20,000 traditional Chinese medicine (TCM) ingredients in hemagglutinin subtype H1 sialic acid binding site found on H1N1 virus. We then performed molecular dynamics simulations to investigate receptor-ligand interaction of the candidates obtained from docking.

Inhibition of peptide aggregation by lipids: Insights from coarse-grained molecular simulations

Andrew Hung [RMIT University], Irene Yarovsky

J. Mol.Graph. and Mod., **29**, 597-607, 2011.

The amyloidogenic peptide apolipoprotein C-II(60–70) is known to exhibit lipid-dependent aggregation behaviour. While the peptide rapidly forms amyloid fibrils in solution, fibrillisation is completely inhibited in the presence of lipids. In order to obtain molecular-level insights into the mechanism of lipid-dependent fibril inhibition, we have employed molecular dynamics simulations in conjunction with a coarse-grained model to study the aggregation of an amyloidogenic peptide, apoC-II(60–70), in the absence and presence of a short-chained lipid, dihexanoylphosphatidylcholine (DHPC).

Prediction of protein binding regions

Naresh Chennamsetty, Vladimir Voynov, Veysel Kayser, Bernhard Helk and Bernhardt L. Trout [Massachusetts Institute of Technology]

Proteins: Stru. Fun. and Bioinfo. **79**, 888–897, 2011

Identifying protein binding sites provides important clues to the function of a protein. Experimental methods to identify the binding sites such as determining the crystal structures of protein complexes are extremely laborious and expensive. Here, we present a computational technique called spatial aggregation propensity (SAP) based on molecular simulations to predict protein binding sites. We apply this technique to two model proteins, an IgG1 antibody and epidermal growth factor receptor (EGFR) and demonstrate that SAP predicts protein binding regions with very good accuracy.

Enzyme Catalysis

Inhibition of secreted phospholipases A₂ by 2-oxoamides based on α -amino acids: Synthesis, in vitro evaluation and molecular docking calculations

Varnavas D. Mouchlis, Victoria Magrioti, Efrosini Barbayianni, Nathan Cermak, Rob C. Oslund, Thomas M. Mavromoustakos, Michael H. Gelb, George Kokotos [University of Athens]

Bioorg. and Med.Chem., **19**, 735-743, 2011.

Group IIA secreted phospholipase A₂ (GIIA sPLA₂) is a member of the mammalian sPLA₂ enzyme family and is associated with various inflammatory conditions. In this study, the synthesis of 2-oxoamides based on α -amino acids and the in vitro evaluation against three secreted sPLA₂s (GIIA, GV and GX) are described. The long chain 2-oxoamide GK126 based on the amino acid (S)-leucine displayed inhibition of human and mouse GIIA sPLA₂s (IC₅₀ 300 nM and 180 nM, respectively).

Enzyme Catalysis (Cont'd)

Enantiospecificity of Chloroperoxidase-Catalyzed Epoxidation: Biased Molecular Dynamics Study of a Cis- β -Methylstyrene/Chloroperoxidase-Compound I Complex

Alexander N. Morozov, Cassian D'Cunha, Carlos A. Alvarez, David C. Chatfield [Florida International University]

Biophysical Journal. **100**, 1066-1075, 2011.

Molecular dynamics simulations of an explicitly solvated cis- β -methylstyrene/chloroperoxidase-Compound I complex are performed to determine the cause of the high enantiospecificity of epoxidation. From the simulations, a two-dimensional free energy potential is calculated to distinguish binding potential wells from which reaction to 1S2R and 1R2S epoxide products may occur. Convergence of the free energy potential is accelerated with an adaptive biasing potential.

Rapid estimation of activation enthalpies for cytochrome-P450-mediated hydroxylations

Arthur N. Mayeno [Colorado State University], Jonathan L. Robinson and Brad Reisfeld

J. Comp. Chem. **32**, 639–657, 2011.

Cytochrome P450 (CYP) enzymes play a critical role in detoxication and bioactivation of xenobiotics; thus, the ability to predict the biotransformation rates and regioselectivity of CYP enzymes toward substrates is an important goal in toxicology and pharmacology. Here, we present the use of the semiempirical quantum chemistry method SAM1 to rapidly estimate relative activation enthalpies ($\Delta H^\ddagger$) for the hydroxylation of aliphatic carbon centers of various substrates.

Long-Range Electrostatic Effects in QM/MM Studies of Enzymatic Reactions: Application of the Solvated Macromolecule Boundary Potential

Tobias Benighaus [Max-Planck-Institut for Kohlenforschung] and Walter Thiel

J. Chem. Theor. and Comp. **7**, 238–249, 2011.

Long-range electrostatic interactions are important in simulations of enzymatic reactions. They can be divided into the effects due to bulk solvent and those due to the electrostatic potential of the outer macromolecule. We study and quantify the importance of these two effects for two test systems by application of the solvated macromolecule boundary potential (SMBP) [*J. Chem. Theory Comput.* **2009**, *5*, 3114–3128]. We validate the accuracy of the SMBP for these test systems and present a transferable protocol for determination of optimal SMBP parameters as well as recommended default values for these parameters.

The effect of calciums on molecular motions of proteinase K

Shu-Qun Liu, Yan Tao, Zhao-Hui Meng, Yun-Xin Fu and Ke-Qin Zhang [Yunnan University]

J. Mol.Mod., **17**, 289-300, 2011.

The native serine protease proteinase K binds two calcium cations. It has been reported that Ca^{2+} removal decreased the enzyme's thermal stability and to some extent the substrate affinity, but has discrepant effects on catalytic activity of the enzyme. Molecular dynamics simulations were performed on the Ca^{2+} -bound and Ca^{2+} -free proteases to investigate the mechanism by which the calciums affect the structural stability, molecular motions, and catalytic activity of proteinase K.

Enzyme Catalysis (Cont'd)

The effect of Li⁺ on GSK-3 inhibition: Molecular dynamics simulation

Hao Sun, Yong-jun Jiang [Zhejiang University], Qing-sen Yu, Cheng-cai Luo and Jian-wei Zou
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J. Mol. Mod., **17**, 377-381, 2011.

Glycogen synthase kinase-3 (GSK-3) is a kind of serine-threonine protein kinase. It places important roles in several signaling pathways and it is a key therapeutic target for a number of diseases, such as diabetes, cancer, Alzheimer's disease and chronic inflammation. Mg²⁺ ions which interact with ATP are conserved in GSK. They are important in phosphoryl transfer. Li⁺ is an inhibitor for GSK-3. It is used to treat bipolar mood disorder. This paper illustrates the effect of Li⁺ on GSK-3. All the results we obtained clearly suggest that inhibition to GSK-3 is caused by the Mg²⁺ replacement with Li⁺.

Computational methods for identifying a layered allosteric regulatory mechanism for ALS-causing mutations of Cu-Zn superoxide dismutase 1

Adam D. Schuyler [University of Connecticut Health Center], Heather A. Carlson and Eva L. Feldman

Proteins: Stru. Fun. and Bioinfo. **79**, 417-427, 2011.

The most prominent form of familial amyotrophic lateral sclerosis (fALS, Lou Gehrig's Disease) is caused by mutations of Cu-Zn superoxide dismutase 1 (SOD1). SOD1 maintains antioxidant activity under fALS causing mutations, suggesting that the mutations introduce a new, toxic, function. Two recently developed computational methods for identifying allosteric control sites are applied to the wild type crystal structure, 4 fALS mutant crystal structures, 20 computationally generated fALS mutants and 1 computationally generated non-fALS mutant.

Structural insights into a low-spin myoglobin variant with bis-histidine coordination from molecular modeling

Ying-Wu Lin [University of South China]

Proteins: Stru. Fun. and Bioinfo. **79**, 679-684, 2011.

Rational design of functional enzymes is a powerful strategy to gain deep insights into more complex native enzymes, such as nitric oxide reductase (NOR). Recently, we engineered a functional model of NOR by creating a two His and one Glu (2-His-1-Glu) non-heme iron center in sperm whale myoglobin (swMb L29E, F43H, H64, called Fe_BMb(-His)). It was found that Fe_BMb(-His) adopts a low-spin state with bis-His coordination in the absence of metal ions binding to the designed metal center.

Membrane Proteins and Lipid Peptide Interactions

Molecular Dynamics Studies of Ion Permeation in VDAC

Huan Rui, Kyu Il Lee, Richard W. Pastor, Wonpil Im [The University of Kansas]

Biophysical Journal. **100**, 602-610, 2011.

The voltage-dependent anion channel (VDAC) in the outer membrane of mitochondria serves an essential role in the transport of metabolites and electrolytes between the cell matrix and mitochondria. To examine its structure, dynamics, and the mechanisms underlying its electrophysiological properties, we performed a total of 1.77 μ s molecular dynamics simulations of human VDAC isoform 1 in DOPE/DOPC mixed bilayers in 1 M KCl solution with transmembrane potentials of 0, ± 25 , ± 50 , ± 75 , and ± 100 mV.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Interaction of Diverse Voltage Sensor Homologs with Lipid Bilayers Revealed by Self-Assembly Simulations

Younes Mokrab, Mark S.P. Sansom [University of Oxford]

Biophysical Journal. **100**, 875-884, 2011.

Voltage sensors (VS) domains couple the activation of ion channels/enzymes to changes in membrane voltage. We used molecular dynamics simulations to examine interactions with lipids of several VS homologs. VSs in intact channels in the activated state are exposed to phospholipids, leading to a characteristic local distortion of the lipid bilayer which decreases its thickness by ~ 10 Å. This effect is mediated by a conserved hydrophilic stretch in the S4-S5 segment linking the VS and the pore domains, and may favor gating charges crossing the membrane.

Velocity-Dependent Mechanical Unfolding of Bacteriorhodopsin Is Governed by a Dynamic Interaction Network

Christian Kappel, Helmut Grubmüller [Max Planck Institute for Biophysical Chemistry]

Biophysical Journal. **100**, 1109-1119, 2011.

Bacteriorhodopsin is a model system for membrane proteins. This seven transmembrane helical protein is embedded within a membrane structure called purple membrane. Its structural stability against mechanical stress was recently investigated by atomic force microscopy experiments, in which single proteins were extracted from the purple membrane. Here, we study this process by all-atom molecular dynamics simulations, in which single bacteriorhodopsin molecules were extracted and unfolded from an atomistic purple membrane model.

25-Hydroxycholesterol Increases the Availability of Cholesterol in Phospholipid Membranes

Brett N. Olsen, Paul H. Schlesinger, Daniel S. Ory, Nathan A. Baker [Pacific Northwest National Laboratory]

Biophysical Journal. **100**, 948-956, 2011.

Side-chain oxysterols are enzymatically generated oxidation products of cholesterol that serve a central role in mediating cholesterol homeostasis. Recent work has shown that side-chain oxysterols, such as 25-hydroxycholesterol (25-HC), alter membrane structure in very different ways from cholesterol, suggesting a possible mechanism for how these oxysterols regulate cholesterol homeostasis. Here we extend our previous work by using molecular-dynamics simulations of 25-HC and cholesterol mixtures in 1-palmitoyl-2-oleoyl-phosphatidylcholine bilayers to examine the combined effects of 25-HC and cholesterol in the same bilayer.

Tropomyosin Position on F-Actin Revealed by EM Reconstruction and Computational Chemistry

Xiaochuan (Edward) Li, Larry S. Tobacman, Ji Young Mun, Roger Craig, Stefan Fischer, William Lehman [Boston University School of Medicine]

Biophysical Journal. **100**, 1005-1013, 2011.

Electron microscopy and fiber diffraction studies of reconstituted F-actin-tropomyosin filaments reveal the azimuthal position of end-to-end linked tropomyosin molecules on the surface of actin. However, the longitudinal z-position of tropomyosin along F-actin is still uncertain. Here, a computational search assessing electrostatic interactions for multiple azimuthal locations, z-positions, and pseudo-rotations of tropomyosin on F-actin was performed.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

VoteDock: Consensus docking method for prediction of protein–ligand interactions

Dariusz Plewczynski [University of Warsaw], Michał Łaźniewski, Marcin Von Grotthuss, Leszek Rychlewski and Krzysztof Ginalski

J. Comp. Chem. **32**, 568–581, 2011.

Molecular recognition plays a fundamental role in all biological processes, and that is why great efforts have been made to understand and predict protein–ligand interactions. Finding a molecule that can potentially bind to a target protein is particularly essential in drug discovery and still remains an expensive and time-consuming task. The purpose of our studies was to present the novel consensus approach to predict both protein–ligand complex structure and its corresponding binding affinity.

Affinity of Four Polar Neurotransmitters for Lipid Bilayer Membranes

Chunhua Wang, Fengbin Ye, Gustavo F. Valardez, Gonther H. Peters, and Peter Westh [Roskilde University]

J. Phys. Chem. B., **115**, 196–203, 2011.

Weak interactions of neurotransmitters and the lipid matrix in the synaptic membrane have been hypothesized to play a role in synaptic transmission of nerve signals, particularly with respect to receptor desensitization. We have used dialysis equilibrium to directly measure the net affinity of selected neurotransmitters for lipid membranes and analyzed this affinity data with respect to calorimetric measurements and molecular dynamics simulations.

Coarse-Grained Molecular Dynamics Simulations of Cobra Cytotoxin A3 Interactions with a Lipid Bilayer: Penetration of Loops into Membranes

Zhi-Yuan Su [Chia Nan University of Pharmacy & Science] and Yeng-Tseng Wang

J. Phys. Chem. B., **115**, 796–802, 2011.

Cobra cytotoxins, which are small three-looped proteins composed of approximately 60 amino acid residues, primarily act by destroying the bilayer membranes of cells and artificial vesicles. However, the molecular mechanism governing this process is not yet completely understood. We used coarse-grained molecular dynamics (CGMD) simulations to study the mechanism underlying the penetration of cardiotoxin A3 (CTX A3), the major toxic component of *Naja atra* (Chinese cobra) venom, into a hydrated 1-palmitoyl-2-oleoyl-1-sn-3-phosphatidylcholine (POPC) lipid bilayer.

Effect of High Pressure on Fully Hydrated DPPC and POPC Bilayers

Rong Chen, David Poger, and Alan E. Mark [The University of Queensland]

J. Phys. Chem. B., **115**, 1038–1044, 2011.

Enhanced hydrostatic pressure can induce phase transitions in hydrated lipid bilayers especially those composed of saturated phospholipids. In this work, the phase behavior of fully hydrated DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphocholine) and POPC (2-oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine) bilayers as a function of pressure up to 3000 atm has been examined in atomic detail on time scales of up to 1.0 μ s, using the molecular dynamics simulation technique.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Interactions of A β 25–35 β -Barrel-like Oligomers with Anionic Lipid Bilayer and Resulting Membrane Leakage: An All-Atom Molecular Dynamics Study

Zhongwen Chang, Yin Luo, Yun Zhang, and Guanghong Wei
[Fudan University]

J. Phys. Chem. B., **115**, 1165–1174, 2011.

A β 25–35, a proteolytic fragment of the Alzheimer amyloid beta (A β) peptide, is produced in the brains of Alzheimer's patients and retains the neurotoxicity of its full-length counterpart. The formation of pores/channels in membranes has been reported as one of the mechanisms responsible for A β 25–35 toxicity. In addition, it has been proposed that pore/channel might be formed by the aggregation of A β 25–35 in membranes into a β -barrel structure. We have investigated the interactions of three types of preformed A β 25–35 β -barrels (labeled as barrels A, B, and C) with negatively charged palmitoyloleoylphosphatidylglycerol (POPG) lipid bilayers using all-atom molecular dynamics (MD) simulations.

Molecular Dynamics Studies of Transportan 10 (Tp10) Interacting with a POPC Lipid Bilayer

Christina M. Dunkin, Antje Pokorny, Paulo F. Almeida, and Hee-Seung Lee [University of North Carolina, Wilmington]

J. Phys. Chem. B., **115**, 1188–1198, 2011.

We performed a series of molecular dynamics simulations to study the nature of interactions between transportan 10 (tp10) and a zwitterionic POPC bilayer. Tp10 is an amphipathic cell-penetrating peptide with a net positive charge of +5 and is known to adopt an α -helical secondary structure on the surface of POPC membranes. The study showed that tp10 preferentially binds to the membrane surface with its hydrophobic side facing the hydrophobic lipid core.

The effects of the L29F mutation on the ligand migration kinetics in crystallized myoglobin as revealed by molecular dynamics simulations

Massimiliano Anselmi, Alfredo Di Nola and Andrea Amadei
[University of Rome "Tor Vergata"]

Proteins: Stru. Fun. and Bioinfo. **79**, 867–879, 2011.

By using multiple molecular dynamics (MD) trajectories, a quantitative description of carbon monoxide (CO) migration within crystal of L29F myoglobin mutant (L29F-Mb) was obtained. The aim was to provide a detailed model for ligand diffusion in the protein to be compared to the available L29F-Mb experimental-computational data and to the corresponding model kinetics we previously obtained for photolyzed CO within crystallized wild-type myoglobin (wt-Mb).

Protein Folding

Molecular Simulations of Mutually Exclusive Folding in a Two-Domain Protein Switch

Brandon M. Mills, Lillian T. Chong [University of Pittsburgh]

Biophysical Journal. **100**, 756–764, 2011.

A major challenge with testing designs of protein conformational switches is the need for experimental probes that can independently monitor their individual protein domains. One way to circumvent this issue is to use a molecular simulation approach in which each domain can be directly observed. Here we report what we believe to be the first molecular simulations of mutually exclusive folding in an engineered two-domain protein switch, providing a direct view of how folding of one protein drives unfolding of the other in a barnase-ubiquitin fusion protein.

Protein Folding (Cont'd)

New Scenarios of Protein Folding Can Occur on the Ribosome

Edward P. O'Brien, John Christodoulou, Michele Vendruscolo, and Christopher M. Dobson [University of Cambridge]

J. Am. Chem. Soc., **133**, 513–526, 2011.

Identifying and understanding the differences between protein folding in bulk solution and in the cell is a crucial challenge facing biology. Using Langevin dynamics, we have simulated intact ribosomes containing five different nascent chains arrested at different stages of their synthesis such that each nascent chain can fold and unfold at or near the exit tunnel vestibule. We find that the native state is destabilized close to the ribosome surface due to an increase in unfolded state entropy and a decrease in native state entropy; the former arises because the unfolded ensemble tends to behave as an expanded random coil near the ribosome and a semicompact globule in bulk solution.

Atomistic Folding Simulations of the Five-Helix Bundle Protein λ_{6-85}

Gregory R. Bowman, Vincent A. Voelz, and Vijay S. Pande [Stanford University]

J. Am. Chem. Soc., **133**, 664–667, 2011.

Protein folding is a classic grand challenge that is relevant to numerous human diseases, such as protein misfolding diseases like Alzheimer's disease. Solving the folding problem will ultimately require a combination of theory, simulation, and experiment, with theory and simulation providing an atomically detailed picture of both the thermodynamics and kinetics of folding and experimental tests grounding these models in reality. . Here we report significant progress toward closing this gap: an atomistic model of the folding of an 80-residue fragment of the λ repressor protein with explicit solvent that captures dynamics on a 10 milliseconds time scale.

Computational Design and Experimental Testing of the Fastest-Folding β -Sheet Protein

Stefano Piana, Krishnarjun Sarkar, Kresten Lindorff-Larsen, Minghao Guo, Martin Gruebele, David E. Shaw [D. E. Shaw Research]

J. Molec. Bio. **405**, 43-48, 2011.

One of the most important and elusive goals of molecular biology is the formulation of a detailed, atomic-level understanding of the process of protein folding. Fast-folding proteins with low free-energy barriers have proved to be particularly productive objects of investigation in this context, but the design of fast-folding proteins was previously driven largely by experiment. Dramatic advances in the attainable length of molecular dynamics simulations have allowed us to characterize in atomic-level detail the folding mechanism of the fast-folding all- β WW domain Fip35.

Stability tests on known and misfolded structures with discrete and all atom molecular dynamics simulations

Sijung Yun, H. Robert Guy [National Institutes of Health, 37 Convent Drive, Bethesda]

J. Mol. Graph. and Mod., **29**, 663-675, 2011.

The brevity of molecular dynamics simulations often limits their utility in developing and evaluating structural models of proteins. The duration of simulations can be increased greatly using discrete molecular dynamics (DMD). However, the trade off is that coarse graining, implicit solvent, and other time-saving procedures reduce the accuracy of DMD simulations. Here we address some of these issues by comparing results of DMD and conventional all atom MD simulations on proteins of known structure and misfolded proteins.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Dominant folding pathways of a peptide chain from ab initio quantum-mechanical simulations

Silvio a Beccara [Università degli Studi di Trento], Pietro Faccioli, Marcello Sega, Francesco Pederiva, Giovanni Garberoglio, and Henri Orland

Jou. Chem. Phys., **134**, 024501, 2011.

Using the dominant reaction pathways method, we perform an ab initio quantum-mechanical simulation of a conformational transition of a peptide chain. The method we propose makes it possible to investigate the out-of-equilibrium dynamics of these systems, without resorting to an empirical representation of the molecular force field. It also allows to study rare transitions involving rearrangements in the electronic structure. By comparing the results of the ab initio simulation with those obtained by employing a standard force field, we discuss its capability to describe the nonequilibrium dynamics of conformational transitions.

Evaluating force field accuracy with long-time simulations of a β -hairpin tryptophan zipper peptide

N. R. Hayre [University of California], R. R. P. Singh, and D. L. Cox

Jou. Chem. Phys., **134**, 035103, 2011.

We have combined graphics processing unit-accelerated all-atom molecular dynamics with parallel tempering to explore the folding properties of small peptides in implicit solvent on the time scale of microseconds. We applied this methodology to the synthetic β -hairpin, trpzip2, and one of its sequence variants, W2W9. Each simulation consisted of over 8 μ s of aggregated virtual time. Several measures of folding behavior showed good convergence, allowing comparison with experimental equilibrium properties.

Identification of folding preferences of cleavage junctions of HIV-1 precursor proteins for regulation of cleavability

Hirotaoka Ode [National Institute of Infectious Diseases, 4-7-1 Gakuen], Masaru Yokoyama, Tadahito Kanda and Hironori Sato

J. Mol.Mod., **17**, 391-399, 2011.

Human immunodeficiency virus type 1 protease (HIV-1 PR) cleaves two viral precursor proteins, Gag and Gag-Pol, at multiple sites. In this study, we used bioinformatics approaches to examine whether the folding preferences of the cleavage junctions influence their cleavabilities by HIV-1 PR. The folding of the eight-amino-acid peptides corresponding to the seven cleavage junctions of the HIV-1_{HXB2} Gag and Gag-Pol precursors were simulated in the PR-free and PR-bound states with molecular dynamics and homology modeling methods, and the relationships between the folding parameters and the reported kinetic parameters of the HIV-1_{HXB2} peptides were analyzed.

Nucleic Acids

Evidence for a Near-Resonant Charge Transfer Mechanism for Double-Stranded Peptide Nucleic Acid

Ravindra Venkatramani, Kathryn L. Davis, Emil Wierzbinski, Silvia Bezer, Alexander Balaeff, Shahar Keinan, Amit Paul, Laura Kocsis, David N. Beratan [Duke University], Catalina Achim, and David H. Waldeck

J. Am. Chem. Soc., **133**, 16862–16872, 2011.

We present evidence for a near-resonant mechanism of charge transfer in short peptide nucleic acid (PNA) duplexes obtained through electrochemical, STM break junction (STM-BJ), and computational studies. A seven base pair (7-bp) PNA duplex with the sequence (TA)₃-(XY)-(TA)₃ was studied, in which XY is a complementary nucleobase pair. The experiments showed that the heterogeneous charge transfer rate constant (k^0) and the single-molecule conductance (σ) correlate with the oxidation potential of the purine base in the XY base pair. A quantitative computational analysis shows that a near-resonant charge transfer regime, wherein a mix of superexchange and hopping mechanisms are expected to coexist, can rationalize all of the experimental results.

Discrimination of Methylcytosine from Hydroxymethylcytosine in DNA Molecules

Meni Wanunu, Devora Cohen-Karni, Robert R. Johnson, Lauren Fields, Jack Benner, Neil Peterman, Yu Zheng, Michael L. Klein, and Marija Drndic [University of Pennsylvania]

J. Am. Chem. Soc., **133**, 486–492, 2011.

Modified DNA bases are widespread in biology. 5-Methylcytosine (mC) is a predominant epigenetic marker in higher eukaryotes involved in gene regulation, development, aging, cancer, and disease. Recently, 5-hydroxymethylcytosine (hmC) was identified in mammalian brain tissue and stem cells. We investigate here the physical properties of DNA with modified cytosines, in efforts to develop a physical tool that distinguishes mC from hmC in DNA fragments. Molecular dynamics simulations reveal that polar cytosine modifications affect internal base pair dynamics, while experimental evidence suggest a correlation between the modified cytosine's polarity, DNA flexibility, and duplex stability.

Interaction identification of Zif268 and TATA_{ZF} proteins with GC-/AT-rich DNA sequence: A theoretical study

Bo Yang, Yanyan Zhu, Yan Wang and Guangju Chen [Beijing Normal University]

J. Comp. Chem. **32**, 416–428, 2011.

Molecular dynamics (MD) simulations for Zif268 (a zinc-finger-protein binding specifically to the GC-rich DNA)-d(A₁G₂C₃G₄T₅G₆G₇G₈C₉A₁₀C₁₁)₂ and TATA_{ZF} (a zinc-finger-protein recognizing the AT-rich DNA)-d(A₁C₂G₃C₄T₅A₆T₇A₈A₉A₁₀A₁₁G₁₂G₁₃)₂ complexes have been performed for investigating the DNA binding affinities and specific recognitions of zinc fingers to GC-rich and AT-rich DNA sequences. The binding free energies for the two systems have been further analyzed by using the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method.

Nucleic Acids (Cont'd)

Dynamical Signature of Abasic Damage in DNA

Kristina E. Furse and Steven A. Corcelli [University of Notre Dame]

J. Am. Chem. Soc., **133**, 720–723, 2011.

The physical interpretation of the long TDSS time scales in biomolecular systems is a matter of considerable debate because of the many different components present in the sample (water, biomolecule, counterions), which have highly correlated motions and intrinsically different abilities to adapt to local perturbations. Here we use molecular dynamics (MD) simulations to show that the surprisingly slow (~ 10 ns) TDSS response of coumarin 102 (C102), a base pair replacement, reflects a distinct dynamical signature for DNA damage.

Nucleic acid sequence design via efficient ensemble defect optimization

Joseph N. Zadeh, Brian R. Wolfe and Niles A. Pierce [California Institute of Technology]

J. Comp. Chem. **32**, 439–452, 2011.

We describe an algorithm for designing the sequence of one or more interacting nucleic acid strands intended to adopt a target secondary structure at equilibrium. Sequence design is formulated as an optimization problem with the goal of reducing the ensemble defect below a user-specified stop condition. For a candidate sequence and a given target secondary structure, the ensemble defect is the average number of incorrectly paired nucleotides at equilibrium evaluated over the ensemble of unpseudoknotted secondary structures.

Relaxed complex scheme suggests novel inhibitors for the lyase activity of DNA polymerase beta

Khaled Barakat [University of Alberta], Jack Tuszynski

J. Mol. Graph. and Mod., **29**, 702–716, 2011.

DNA polymerase beta (pol β), the error-prone polymerase of base excision repair, plays a significant role in chemotherapeutic agent resistance. Its over expression reduces the efficacy of anticancer drug therapies including ionizing radiation, bleomycin, monofunctional alkylating agents and cisplatin. Here, we applied the relaxed complex scheme virtual screening (RCSVS) to allow for the full receptor flexibility in filtering the NCI diversity set, DrugBank compounds and a library of ~ 9000 fragmental compounds for novel pol β inhibitors.

Exploring the conformational changes of the ATP binding site of gyrase B from Escherichia coli complexed with different established inhibitors by using molecular dynamics simulation: Protein–ligand interactions in the light of the alanine scanning and free energy decomposition methods

Liane Saíz-Urra, Miguel Angel Cabrera, Matheus Froeyen [Katholieke Universiteit Leuven]

J. Mol. Graph. and Mod., **29**, 726–739, 2011.

DNA gyrase is a well-established antibacterial target consisting of two subunits, GyrA and GyrB, in a heterodimer A_2B_2 . GyrA is involved in DNA breakage and reunion and GyrB catalyzes the hydrolysis of ATP. The GyrB subunit from Escherichia coli has been investigated, namely the ATP binding pocket both considering the protein without ligands and bound with the inhibitors clorobiocin, novobiocin and 5'-adenylyl- β - γ -imidodiphosphate. The stability of the systems was studied by molecular dynamics simulation with the further analysis of the time dependent root-mean-square coordinate deviation (RMSD) from the initial structure, and temperature factors.

Nucleic Acids (Cont'd)

Binding Selectivity of RecA to a single stranded DNA, a computational approach

Claudio Carra [Universities Space Research Association, 2101 NASA Parkway] and Francis A. Cucinotta

J. Mol.Mod., **17**, 133-150, 2011.

Homologous recombination (HR) is the major DNA double strand break repair pathway which maintains the genomic integrity. It is fundamental for the survivability and functionality of all organisms. One of the initial steps in HR is the formation of the nucleoprotein filament composed by a single stranded DNA chain surrounded by the recombinases protein. Our theoretical study was aimed at elucidating the selectivity of the interaction between a monomer of the recombinases enzyme in the *Escherichia coli*, EcRecA, the bacterial homologue of human Rad51, with a series of oligonucleotides of nine bases length.

Virtual screening of specific chemical compounds by exploring *E.coli* NAD⁺-dependent DNA ligase as a target for antibacterial drug discovery

Bashir Akhlaq Akhoun [Punjabi University, Patiala], Shishir K Gupta, Gagan Dhaliwal, Mugdha Srivastava and Shailendra K Gupta

J. Mol.Mod., **17**, 265-273, 2011.

Unique substrate specificity compared with ATP-dependent human DNA ligases recommends *E.coli* NAD⁺-ligases as potential targets. A plausible strategy is to identify the structural components of bacterial DNA ligase that interact with NAD⁺ and then to isolate small molecules that recognize these components and thereby block the binding of NAD⁺ to the ligase. This work describes a molecular modeling approach to detect the 3D structure of NAD⁺-dependent DNA ligase in *E. coli* whose partial structure was determined by wet lab experiments and rest structure was left as such on the road for repairment.

A Coarse-Grained Model of DNA with Explicit Solvation by Water and Ions

Robert C. DeMille, Thomas E. Cheatham, III, and Valeria Molinero [University of Utah]

J. Phys. Chem. B., **115**, 132-142, 2011.

Solvation by water and ions has been shown to be vitally important for biological molecules, yet fully atomistic simulations of large biomolecules remain a challenge due to their high computational cost. The effect of solvation is the most pronounced in polyelectrolytes, of which DNA is a paradigmatic example. Coarse-grained (CG) representations have been developed to model the essential physics of the DNA molecule, yet almost without exception, these models replace the water and ions by implicit solvation in order to significantly reduce the computational expense. This work introduces the first coarse-grained model of DNA solvated explicitly with water and ions.

DNA Compaction by a Dendrimer

Bidisha Nandy and Prabal K. Maiti [Indian Institute of Science]

J. Phys. Chem. B., **115**, 217-230, 2011.

At physiological pH, a PAMAM dendrimer is positively charged and can effectively bind negatively charged DNA. Currently, there has been great interest in understanding this complexation reaction both for fundamental (as a model for complex biological reactions) as well as for practical (as a gene delivery material and probe for sensing DNA sequence) reasons. Here, we have studied the complexation between double-stranded DNA and various generations of PAMAM dendrimers (G3-G5) through atomistic molecular dynamics simulations in the presence of water and ions.

Surfaces, Catalysts, and Materials Subjects

Competitive Adsorption of Surfactants and Polymers at the Free Water Surface. A Computer Simulation Study of the Sodium Dodecyl Sulfate–Poly(ethylene oxide) System

Maria Darvas, Tibor Gilanyi, and Pal Jedlovsky [Eotvos Lorand University]

J. Phys. Chem. B., **115**, 933–944, 2011.

Competitive adsorption of a neutral amphiphilic polymer, namely poly(ethylene oxide) (PEO) and an ionic surfactant, i.e., sodium dodecyl sulfate (SDS), is investigated at the free water surface by computer simulation methods at 298 K. The sampled equilibrium configurations are analyzed in terms of the novel identification of the truly interfacial molecules (ITIM) method, by which the intrinsic surface of the aqueous phase (i.e., its real surface corrugated by the capillary waves) instead of an ideally flat surface approximating its macroscopic surface plane, can be taken into account.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Receptor-dependent (RD) 3D-QSAR approach of a series of benzylpiperidine inhibitors of human acetylcholinesterase (HuAChE)

Jocley Queiroz Araújo, Monique Araújo de Brito, Lucas Villas Bôas Hoelz, Ricardo Bicca de Alencastro, Helena Carla Castro, Carlos Rangel Rodrigues, Magaly Girão Albuquerque [Laboratório de Modelagem Molecular (LabMMol)]

European J. of Med. Chem., **46**, 39-51, 2011.

Acetylcholine inhibitors (AChEIs) are currently considered as potential drugs for treating Alzheimer disease. In this work, we developed a receptor-dependent 3D-QSAR (RD-3D-QSAR) models based on a series of 60 benzylpiperidine inhibitors of human acetylcholinesterase to support the design of new AChEIs. The best two models, A–F (N = 47, $q^2 = 0.736$, $r^2 = 0.860$) and C–F (N = 47, $q^2 = 0.753$, $r^2 = 0.900$) were developed and validated by a combined GA-PLS approach, available in WOLF.

Predicting hERG activities of compounds from their 3D structures: Development and evaluation of a global descriptors based QSAR model

Nandita Sinha, Srikanta Sen [Bengal Intelligent Park]

European J. of Med. Chem., **46**, 618-630, 2011.

A QSAR based predictive model of hERG activity in terms of ‘global descriptors’ has been developed and evaluated. The QSAR was developed by training 77 compounds covering a wide range of activities and was validated based on an external ‘test set’ of 80 compounds using neural network method. Statistical parameters and examination of enrichment factor indicated the effectiveness of the present model. Randomization test demonstrated the robustness of the model and cross-validation test further validated the QSAR.

Quantitative Structure-Activity Relations (Cont'd)

An application of two MIFs-based tools (Volsurf+ and Pentacle) to binary QSAR: The case of a palinurin-related data set of non-ATP competitive Glycogen Synthase Kinase 3 β (GSK-3 β) inhibitors

Giuseppe Ermondi, Giulia Caron [Universidade de Vigo], Isela Garcia Pintos, Michela Gerbaldo, Manuel Pérez, Daniel I. Pérez, Zoila Gándara, Ana Martínez, Generosa Gómez, Yagamare Fall

European J. of Med. Chem., **46**, 860-869, 2011.

VolSurf+ and GRIND descriptors extract the information present in MIFs calculated by GRID: the first are simpler to interpret and generally applied to ADME-Tox topics, whereas the latter are more sophisticated and thus more suited for pharmacodynamics events. Here we present a study which compares binary QSAR models obtained with VolSurf+ descriptors and GRIND for a data set of non-ATP competitive GSK-3 β inhibitors chemically related to palinurin for which the biological activity is expressed in binary format.

Development of quantitative structure-activity relationships for explanatory modeling of fast reacting (meth)acrylate monomers bearing novel functionality

Jason A. Morrill [William Jewell College], Joedd H. Biggs, Christopher N. Bowman, Jeffrey W. Stansbury

J. Mol. Graph. and Mod., **29**, 763-772, 2011.

The photoinitiated polymerization of (meth)acrylate monomers bearing novel carbamate functionality exhibits significantly greater reaction rate when compared to more traditional acrylate monomers undergoing similar polymerization. This unusually fast reactivity has been the subject of much investigation. In order to suggest an explanatory mechanism for the enhanced polymerization rates we have conducted quantitative structure-activity relationship investigations of these novel monomers.

Potentials and Parameters

Statistical approaches to forcefield calibration and prediction uncertainty in molecular simulation

Fabien Cailliez [Laboratoire de Chimie Physique, UMR8000, CNRS/Univ] and Pascal Pernot

Jou. Chem. Phys., **134**, 054124, 2011.

Calibration of forcefields for molecular simulation should account for the measurement uncertainty of the reference dataset and for the model inadequacy, i.e., the inability of the force-field/simulation pair to reproduce experimental data within their uncertainty range. In all rigour, the resulting uncertainty of calibrated force-field parameters is a source of uncertainty for simulation predictions. Various calibration strategies and calibration models within the Bayesian calibration/prediction framework are explored in the present article.

Molecular Simulations of Dodecyl- β -maltoside Micelles in Water: Influence of the Headgroup Conformation and Force Field Parameters

Stephane Abel [DSV/iBiTEC-S/SB²SM/LBMS & CNRS URA 2096, entre d'Etudes, Saclay], Francois-Yves Dupradeau, E. Prabhu Raman, Alexander D. MacKerell, Jr., and Massimo Marchi

J. Phys. Chem. B., **115**, 487-499, 2011.

This paper deals with the development and validation of new potential parameter sets, based on the CHARMM36 and GLYCAM06 force fields, to simulate micelles of the two anomeric forms (α and β) of N-dodecyl- β -maltoside (C₁₂G₂), a surfactant widely used in the extraction and purification of membrane proteins. In this context, properties such as size, shape, internal structure, and hydration of the C₁₂G₂ anomer micelles were thoroughly investigated by molecular dynamics simulations and the results compared with experiments. Finally, we show that depending on the potential the water translational diffusion of the interfacial water is 7-11.5 times slower than that of bulk water due to the entrapment of the water in the micelle crevices.

Molecular Dynamics

Brownian Dynamics Simulations of Ion Transport through the VDAC

Kyu Il Lee, Huan Rui, Richard W. Pastor, Wonpil Im [The University of Kansas]

Biophysical Journal. **100**, 611-619, 2011.

It is important to gain a physical understanding of ion transport through the voltage-dependent anion channel (VDAC) because this channel provides primary permeation pathways for metabolites and electrolytes between the cytosol and mitochondria. We performed grand canonical Monte Carlo/Brownian dynamics (GCMC/BD) simulations to explore the ion transport properties of human VDAC isoform 1 (hVDAC1; PDB:2K4T) embedded in an implicit membrane.

Molecular dynamics simulations of aqueous ions at the liquid-vapor interface accelerated using graphics processors

Brad A. Bauer, Joseph E. Davis, Michela Taufer [University of Delaware] and Sandeep Patel

J. Comp. Chem. **32**, 187–195, 2011.

Molecular dynamics (MD) simulations are a vital tool in chemical research, as they are able to provide an atomistic view of chemical systems and processes that is not obtainable through experiment. However, large-scale MD simulations require access to multicore clusters or supercomputers that are not always available to all researchers. Here, we present results of GPU-accelerated simulations of the liquid-vapor interface of aqueous sodium iodide solutions. Analysis of various properties, such as density and surface tension, demonstrates that our model is consistent with previous studies of similar systems.

Molecular dynamics simulations of aqueous ions at the liquid-vapor interface accelerated using graphics processors

Brad A. Bauer, Joseph E. Davis, Michela Taufer [University of Delaware] and Sandeep Patel

J. Comp. Chem. **32**, 187–195, 2011.

The influence of the total number of cores, the number of cores dedicated to Particle mesh Ewald (PME) calculation and the choice of single vs. double precision on the performance of molecular dynamic (MD) simulations in the size of 70,000 to 1.7 million of atoms was analyzed on three different high-performance computing facilities employing GROMACS 4 by running about 6000 benchmark simulations. Small and medium sized systems scaled linear up to 64 and 128 cores, respectively.

Simple and effective application of the Wang-Landau method for multicanonical molecular dynamics simulation

Hiromitsu Shimoyama [Osaka University], Haruki Nakamura, and Yasushige Yonezawa

Jou. Chem. Phys., **134**, 024109, 2011.

We propose a novel application of the Wang-Landau method (WLM) for multicanonical molecular dynamics (McMD) simulations. Originally, WLM was developed for Monte Carlo (MC) simulations. Fundamentally, WLM remarkably reduces simulation efforts because it estimates the optimal multicanonical energy function automatically. When WLM is applied to McMD, not only the multicanonical energy but also energy gradient must be estimated adequately.

Molecular Dynamics (Cont'd)

Effects of ionic strength on SAXS data for proteins revealed by molecular dynamics simulations

Tomotaka Oroguchi [Yokohama City University] and Mitsunori Ikeguchi

Jou. Chem. Phys., **134**, 025102, 2011.

The combination of small-angle X-ray solution scattering (SAXS) experiments and molecular dynamics (MD) simulations is now becoming a powerful tool to study protein conformations in solution at an atomic resolution. In this study, we investigated effects of ionic strength on SAXS data theoretically by using MD simulations of hen egg white lysozyme at various NaCl concentrations from 0 to 1 M. The calculated SAXS excess intensities showed a significant dependence on ion concentration, which originates from the different solvent density distributions in the presence and absence of ions.

Monte Carlo

Quality of random number generators significantly affects results of Monte Carlo simulations for organic and biological systems

Timothy H. Click, Aibing Liu and George A. Kaminski [Worcester Polytechnic Institute]

J. Comp. Chem. **32**, 513–524, 2011.

We have simulated pure liquid butane, methanol, and hydrated alanine polypeptide with the Monte Carlo technique using three kinds of random number generators (RNG's)—the standard Linear Congruential Generator (LCG), a modification of the LCG with additional randomization used in the BOSS software, and the “Mersenne Twister” generator by Matsumoto and Nishimura. While using the latter two RNG's leads to reasonably similar physical features, the LCG produces significant different results.

Optimization of Monte Carlo trial moves for protein simulations

Marcos R. Betancourt [Purdue University]

Jou. Chem. Phys., **134**, 014104, 2011.

Closed rigid-body rotations of residue segments under bond-angle restraints are simple and effective Monte Carlo moves for searching the conformational space of proteins. The efficiency of these moves is examined here as a function of the number of moving residues and the magnitude of their displacement. It is found that the efficiency of folding and equilibrium simulations can be significantly improved by tailoring the distribution of the number of moving residues to the simulation temperature.

A simple methodology for analyzing association effects on response functions via Monte Carlo simulations

P. Gómez-Álvarez [University of Vigo], A. Dopazo-Paz, L. Romani, and D. González-Salgado

Jou. Chem. Phys., **134**, 014104, 2011.

A simple methodology was developed to analyze association effects on the thermodynamic response functions for a pure self-associated fluid via Monte Carlo simulations. The procedure essentially involves expressing the residual energy and volume of the fluid in terms of these properties for two hypothetical fluids consisting of monomers and associated molecules, respectively. This allows the thermodynamic response functions to be expressed in a perturbative form as a combination of the values for the property in the monomeric fluid and the contribution of association (the perturbative term).

Monte Carlo (Cont'd)

Modeling gas permeation through membranes by kinetic Monte Carlo: Applications to H₂, O₂, and N₂ in hydrated Nafion[®]

Gert Dorenbos [Knowledgenet Co., Lofty Chuo Bldg.] and Kei Morohoshi

Jou. Chem. Phys., **134**, 044133, 2011.

We present a simulation tool in order to predict gas permeation through heterogeneous, microphase separated structures. The method combines dissipative particle dynamics (DPD) with kinetic Monte Carlo (KMC). Morphologies obtained from DPD are mapped onto a high density grid on which gas diffusion takes place. Required input parameters for the KMC calculations are the gas solubility and gas diffusion constant within each of the pure phase components.

Surface tension of water–alcohol mixtures from Monte Carlo simulations

F. Biscay [Université Blaise Pascal], A. Ghoufi, and P. Malfreyt

Jou. Chem. Phys., **134**, 044709, 2011.

Monte Carlo simulations are reported to predict the dependence of the surface tension of water–alcohol mixtures on the alcohol concentration. Alcohols are modeled using the anisotropic united atom model recently extended to alcohol molecules. The molecular simulations show a good agreement between the experimental and calculated surface tensions for the water–methanol and water–propanol mixtures. This good agreement with experiments is also established through the comparison of the excess surface tensions.

Reaction Ensemble Monte Carlo Simulation of Complex Molecular Systems

Thomas W. Rosch and Edward J. Maginn [University of Notre Dame]

J. Chem. Theor. and Comp., **7**, 269–279, 2011.

Acceptance rules for reaction ensemble Monte Carlo (RxMC) simulations containing classically modeled atomistic degrees of freedom are derived for complex molecular systems where insertions and deletions are achieved gradually by utilizing the continuous fractional component (CFC) method. A self-consistent manner in which to utilize statistical mechanical data contained in ideal gas free energy parameters during RxMC moves is presented.

Free Energy Perturbation

Free energy perturbation approach for the rational engineering of the antibody for human hepatitis B virus

Hwangseo Park, Young Ho Jeon [Korea Basic Science Institute]

J. Mol. Graph. and Mod., **29**, 643–649, 2011.

HxKR127 is the humanized monoclonal antibody effective for the neutralization of human hepatitis B virus. By means of the free energy perturbation (FEP) calculations based on molecular dynamic (MD) simulations, we examine the mutation-induced variations in the energetic and structural features associated with the interactions between HxKR127 and its antigen. N58A, Y96A, D97A, and D97A/Y102A mutants of HxKR127 are taken in account in this study for which the experimental data for relative efficacies with respect to the wild-type antibody are available.

Free Energy Perturbation (Cont'd)

A Generalized Free Energy Perturbation Theory Accounting for End States with Differing Configuration Space Volume

R. Thomas Ullmann [University of Bayreuth] and G. Matthias Ullmann

J. Phys. Chem. B., **115**, 507–521, 2011.

We present a generalized free energy perturbation theory that is inspired by Monte Carlo techniques and based on a microstate description of a transformation between two states of a physical system. It is shown that the present free energy perturbation theory stated by the Zwanzig equation follows as a special case of our theory. Our method uses a stochastic mapping of the end states that associates a given microstate from one ensemble with a microstate from the adjacent ensemble according to a probability distribution.

QM and QM/MM

Autocatalytic Intramolecular Isopeptide Bond Formation in Gram-Positive Bacterial Pili: A QM/MM Simulation

Xiangqian Hu, Hao Hu, Jeffrey A. Melvin, Kathleen W. Clancy, Dewey G. McCafferty [Duke University], and Weitao Yang

J. Am. Chem. Soc., **133**, 478–485, 2011.

Genome-wide analyses of pili-containing Gram-positive bacteria are known or suspected to contain isopeptide bonds in pilin subunits. However, the chemical mechanism of how isopeptide bonds form within pilin remains poorly understood. We used the QM/MM minimum free-energy path method to examine the reaction details of forming the isopeptide bonds with Spy0128 as a model pilin, specifically focusing on the role of the glutamate in catalysis.

Molecular dynamics simulations of aqueous ions at the liquid–vapor interface accelerated using graphics processors

Brad A. Bauer, Joseph E. Davis, Michela Taufer [University of Delaware] and Sandeep Patel

J. Comp. Chem. **32**, 187–195, 2011.

Intramolecular interactions between fragments of L-phenylalanine, i.e., phenyl and alaninyl, have been investigated using dual space analysis (DSA) quantum mechanically. Valence space photoelectron spectra (PES), orbital energy topology and correlation diagram, as well as orbital momentum distributions (MDs) of L-phenylalanine, benzene and L-alanine are studied using density functional theory methods.

Solvent effect on the absorption spectra of coumarin 120 in water: A combined quantum mechanical and molecular mechanical study

Tetsuya Sakata [Kyushu University], Yukio Kawashima, and Haruyuki Nakano

Jou. Chem. Phys., **134**, 014501, 2011.

The solvent effect on the absorption spectra of coumarin 120 (C120) in water was studied utilizing the combined quantum mechanical/molecular mechanical (QM/MM) method. In molecular dynamics (MD) simulation, a new sampling scheme was introduced to provide enough samples for both solute and solvent molecules to obtain the average physical properties of the molecules in solution. We sampled the structure of the solute and solvent molecules separately. First, we executed a QM/MM MD simulation, where we sampled the solute molecule in solution.

QM and QM/MM (Cont'd)

Implementation of the analytic energy gradient for the combined time-dependent density functional theory/effective fragment potential method: Application to excited-state molecular dynamics simulations

Noriyuki Minezawa [Iowa State University], Nuwan De Silva, Federico Zahariev, and Mark S. Gordon

Jou. Chem. Phys., **134**, 054111, 2011.

Excited-state quantum mechanics/molecular mechanics molecular dynamics simulations are performed, to examine the solvent effects on the fluorescence spectra of aqueous formaldehyde. For that purpose, the analytical energy gradient has been derived and implemented for the linear-response time-dependent density functional theory (TDDFT) combined with the effective fragment potential (EFP) method. The EFP method is an efficient ab initio based polarizable model that describes the explicit solvent effects on electronic excitations, in the present work within a hybrid TDDFT/EFP scheme.

Protein Free Energy Corrections in ONIOM QM:MM Modeling: A Case Study for Isopenicillin N Synthase (IPNS)

Tsutomu Kawatsu, Marcus Lundberg, and Keiji Morokuma [Kyoto University]

J. Chem. Theor. and Comp., **7**, 390–401, 2011.

The protein environment can have significant effects on the enzyme catalysis even though the reaction occurs locally at the reaction center. In this paper, we describe an efficient scheme that includes a classical molecular dynamics (MD) free-energy perturbation (FEP) correction to the reaction energy diagram, as a complement to the protein effect obtained from static ONIOM (QM:MM) calculations. The method is applied to eight different reaction steps, from the O₂-bound reactant to formation of a high-valent ferryl-oxo intermediate, in the nonheme iron enzyme isopenicillin N synthase (IPNS), for which the QM:MM energy diagram has previously been computed.

Efficient Calculation of QM/MM Frequencies with the Mobile Block Hessian

An Ghysels [Ghent University], H. Lee Woodcock, III, Joseph D. Larkin, Benjamin T. Miller, Yihan Shao, Jing Kong, Dimitri Van Neck, Veronique Van Speybroeck, Michel Waroquier, and Bernard R. Brooks

J. Chem. Theor. and Comp., **7**, 496–514, 2010.

The calculation of the analytical second derivative matrix (Hessian) is the bottleneck for vibrational analysis in QM/MM systems when an electrostatic embedding scheme is employed. This paper presents an extension to the Mobile Block Hessian (MBH) formalism for QM/MM calculations with blocks in the MM region and its implementation in a parallel version of the Q-Chem/CHARMM interface. MBH reduces both the CPU time and the memory requirements compared to the standard full Hessian QM/MM analysis, without the need to use a cutoff distance for the electrostatic interactions.

QM/MM Free Energy Simulations of Salicylic Acid Methyltransferase: Effects of Stabilization of TS-like Structures on Substrate Specificity

Jianzhuang Yao, Qin Xu, Feng Chen, and Hong Guo [University of Tennessee]

J. Phys. Chem. B., **115**, 389–396, 2011.

Salicylic acid methyltransferases (SAMTs) synthesize methyl salicylate (MeSA) using salicylate as the substrate. MeSA synthesized in plants may function as an airborne signal to activate the expression of defense-related genes and could also be a critical mobile signaling molecule that travels from the site of plant infection to establish systemic immunity in the induction of disease resistance. Here the results of QM/MM free energy simulations for the methyl transfer process in *Clarkia breweri* SAMT (CbSAMT) are reported to determine the origin of the substrate specificity of SAMTs.

Comparative or Homology Modeling

Studying the catechol binding cavity in comparative models of human dopamine D₂ receptor

Amirhossein Sakhteman [University of Eastern Finland],
Maija Lahtela-Kakkonen, Antti Poso

J. Mol. Graph. and Mod., **29**, 685-69, 2011.

Obtaining more structural information of human dopamine D₂ receptor may help in the design of better therapeutic agents against diseases such as Parkinsons. In this study attempts have been made to develop a functional model for the catechol binding site of the human dopamine D₂ receptor, with two primary models being postulated based on the presence of a disulfide bridge in the second extracellular loop. The models have been subjected to subsequent molecular dynamics simulation and receptor based virtual screening of catechol structures.

Optimal molecular structures of prion AGAAAAGA amyloid fibrils formatted by simulated annealing

Jiapu Zhang [The University of Melbourne]

J. Mol. Mod., **17**, 173-179, 2011.

To date, there is little structural data available on the AGAAAAGA palindrome in the hydrophobic region (113–120) of prion proteins, although many experimental studies have shown that this region has amyloid fibril forming properties. This region belongs to the N-terminal unstructured region (1–123) of prions, the structure of which has proved hard to determine using NMR or X-ray crystallography. This paper reports the successful construction of three amyloid fibril models for this region.

Structure of the Chromophore Binding Pocket in the Pr State of Plant Phytochrome phyA

Maria Andrea Mroginski [Technische Universitat Berlin],
Steve Kaminski, David von Stetten, Simone Ringsdorf,
Wolfgang Gärtner, Lars-Oliver Essen, and Peter Hildebrandt

J. Phys. Chem. B., **115**, 132–142, 2011.

A homology structural model was generated for plant phytochrome phyA utilizing the crystal structure of the sensory module of cyanobacterial phytochrome Cph1 (Cph1Δ2). As chromophores, either the native phytychromobilin cofactor (PΦB) or phycocyanobilin (PCB), the natural cofactor in Cph1, was incorporated. These homology models were further optimized by molecular dynamics (MD) simulations revealing a satisfying overall agreement with the crystal structure of Cph1Δ2.

Ligand Docking

A novel computational approach “BP-STOCH” to study ligand binding to finite lattice

Daria A. Beshnova, Ekaterina G. Bereznyak, Anna V. Shestopalova and Maxim P. Evstigneev [Sevastopol National Technical University]

Biopolymers. **95**, 208–216, 2011.

We report a novel computational algorithm “BP-STOCH” to be used for studying single-type ligand binding with biopolymers of finite lengths, such as DNA oligonucleotides or oligopeptides. It is based on an idea to represent any type of ligand–biopolymer complex in a form of binary number, where “0” and “1” bits stand for vacant and engaged monomers of the biopolymer, respectively.

Ligand Docking (Cont'd)

Mechanisms of Protein-Ligand Association and Its Modulation by Protein Mutations

Martin Held, Philipp Metzner, Jan-Hendrik Prinz, Frank Noé [Freie Universität Berlin]

Biophysical Journal. 100, 701-710, 2011.

Protein-ligand interactions are essential for nearly all biological processes, and yet the biophysical mechanism that enables potential binding partners to associate before specific binding occurs remains poorly understood. To address these questions, we developed a computational approach to systematically analyze the complete ensemble of association pathways. Here, we use this approach to study the binding of a phosphate ion to the Escherichia coli phosphate-binding protein.

A simulation strategy for the atomistic modeling of flexible molecules covalently tethered to rigid surfaces: Application to peptides

David Curcó [Universitat de Barcelona], David Zanuy, Ruth Nussinov and Carlos Alemán

J. Comp. Chem. **32**, 607-619, 2011.

A computational strategy to model flexible molecules tethered to a rigid inert surface is presented. The strategy is able to provide uncorrelated relaxed microstructures at the atomistic level. It combines an algorithm to generate molecules tethered to the surface without atomic overlaps, a method to insert solvent molecules and ions in the simulation box, and a powerful relaxation procedure.

Docking-based virtual screening for ligands of G protein-coupled receptors: Not only crystal structures but also in silico models

Santiago Vilar, Giulio Ferino, Sharangdhar S. Phatak, Barkin Berk, Claudio N. Cavasotto, Stefano Costanzi [National Institutes of Health, DHHS, Bethesda]

J. Mol. Graph. and Mod., **29**, 614-623, 2011.

G protein-coupled receptors (GPCRs) regulate a wide range of physiological functions and hold great pharmaceutical interest. Using the β_2 -adrenergic receptor as a case study, this article explores the applicability of docking-based virtual screening to the discovery of GPCR ligands and defines methods intended to improve the screening performance. Our controlled computational experiments were performed on a compound dataset containing known agonists and blockers of the receptor as well as a large number of decoys.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 29 (5), January 2011.

591-596 **How do carbon nanotubes serve as carriers for gemcitabine transport in a drug delivery system?**, Uthumporn Arsawang, Oraphan Saengsawang, Thanyada Rungrotmongkol, Purinchaya Sornmee, Kitiyaporn Wittayanarakul, Tawun Remsungnen, Supot Hannongbua [Chulalongkorn University]

See Applications / Carbon Nanotubes.

597-607 **Inhibition of peptide aggregation by lipids: Insights from coarse-grained molecular simulations**, Andrew Hung [RMIT University], Irene Yarovsky

See Applications / Membrane proteins and Lipid-Peptide Interactions.

608-613 **2,4-Diamino-5-(2'-arylpropargyl)pyrimidine derivatives as new nonclassical antifolates for human dihydrofolate reductase inhibition**, Oztekin Algul, Janet L. Paulsen, Amy C. Anderson [University of Connecticut]

See Applications / Medicinal Chemistry and Drug Design.

614-623 **Docking-based virtual screening for ligands of G protein-coupled receptors: Not only crystal structures but also in silico models**, Santiago Vilar, Giulio Ferino, Sharangdhar S. Phatak, Barkin Berk, Claudio N. Cavasotto, Stefano Costanzi [National Institutes of Health, DHHS, Bethesda]

See Methodology / Ligand Docking.

624-634 **Understanding the effects of carbocyclic sugars constrained to north and south conformations on RNA nanodesign**, Taejin Kim, Joseph J. Barchi Jr., Victor E. Marquez, Bruce A. Shapiro [National Cancer Institute at Frederick]

Relatively new types of the modified nucleotides, namely carbocyclic sugars that are constrained to north or south (C2' or C3' exo) conformations, can be used for RNA nanoparticle design to control their structures and stability by rigidifying nucleotides and altering the helical properties of RNA duplexes.

635-642 **Structural characterization and substrate specificity of VpAAT1 protein related to ester biosynthesis in mountain papaya fruit**, Luis Morales-Quintana, Lida Fuentes, Carlos Gaete-Eastman, Raúl Herrera, María Alejandra Moya-León [Universidad de Talca]

In order to understand the molecular mechanism involved in the production of esters in this fruit, an AAT gene which has been previously cloned and characterized from mountain papaya (VpAAT1) was expressed in yeasts, and the highest enzyme activity of the recombinant protein was obtained when the enzyme was tested for its ability to produce benzyl acetate.

- 643-649 **Free energy perturbation approach for the rational engineering of the antibody for human hepatitis B virus**, Hwangseo Park, Young Ho Jeon [Korea Basic Science Institute]

See Methodology / Free energy Perturbations.

- 650-656 **Differences in active-site microarchitecture explain the dissimilar behaviors of PBP5 and 6 in Escherichia coli**, Chiranjit Chowdhury, Anindya S. Ghosh [Indian Institute of Technology, Kharagpur]

See Applications / Protein Dynamics.

- 657-662 **Analysis of the stabilities of hexameric amyloid- β (1-42) models using discrete molecular dynamics simulations**, Sijung Yun, Sajung Yun, H. Robert Guy [National Institutes of Health, 37 Convent Drive, Bethesda]

See Applications / Protein Dynamics.

- 663-675 **Stability tests on known and misfolded structures with discrete and all atom molecular dynamics simulations**, Sijung Yun, H. Robert Guy [National Institutes of Health, 37 Convent Drive, Bethesda]

See Applications / Protein Folding.

- 676-684 **Improving the description of salt bridge strength and geometry in a Generalized Born model**, Yi Shang [Stony Brook University], Hai Nguyen, Lauren Wickstrom, Asim Okur, Carlos Simmerling

The Generalized Born (GB) solvent model is widely used in molecular dynamics simulations because it can be less computationally expensive and it samples conformational changes more efficiently than explicit solvent simulations. Here we present our finding that similar correction also shows dramatic improvement for the AMBER GB-OBC solvent model.

- 685-692 **Studying the catechol binding cavity in comparative models of human dopamine D₂ receptor**, Amirhossein Sakhteman [University of Eastern Finland], Maija Lahtela-Kakkonen, Antti Poso

See Methodology / Homology Modeling.

- 693-701 **Computational investigation of interactions between human H₂ receptor and its agonists**, Xianqiang Sun, Yaozong Li, Weihua Li, Zhejun Xu, Yun Tang [East China University of Science and Technology]

See Applications / Medicinal Chemistry and Drug Design.

- 702-716 **Relaxed complex scheme suggests novel inhibitors for the lyase activity of DNA polymerase beta**, Khaled Barakat [University of Alberta], Jack Tuszynski

See Applications / Nucleic Acids.

- 717-725 **Density functional theory studies on the structures and electronic communication of meso-ferrocenylporphyrins: Long range orbital coupling via porphyrin core**, Lijuan Zhang, Dongdong Qi, Yuexing Zhang, Yongzhong Bian, Jianzhuang Jiang [University of Science and Technology Beijing]

The molecular and electronic structures together with the electronic absorption spectra of a series of metal free meso-ferrocenylporphyrins, namely 5-ferrocenylporphyrin (1), 5,10-diferrocenylporphyrin (2), 5,15-diferrocenylporphyrin (3), 5,10,15-triferrocenylporphyrin (4), and 5,10,15,20-tetraferrocenylporphyrin (5) have been studied with the density functional theory (DFT) and time-dependent density functional theory (TD-DFT) methods.

- 726-739 **Exploring the conformational changes of the ATP binding site of gyrase B from Escherichia coli complexed with different established inhibitors by using molecular dynamics simulation: Protein–ligand interactions in the light of the alanine scanning and free energy decomposition methods**, Liane Saíz-Urra, Miguel Angel Cabrera, Matheus Froeyen [Katholieke Universiteit Leuven]

See Applications / Nucleic Acids.

- 740-746 **Protein modeling and active site binding mode interactions of myrosinase–sinigrin in Brassica juncea—An in silico approach**, Rajender Kumar [CCSHAU, Hisar], Sandeep Kumar, Seema Sangwan, Inderjit Singh Yadav, Rakesh Yadav

See Applications / Homology Modeling.

- 747-762 **Studies of tricyclic piperazine/piperidine furnished molecules as novel integrin $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ dual antagonists using 3D-QSAR and molecular docking**, Yulian Yan, Yan Li [Dalian University of Technology], Shuwei Zhang, Chunzhi Ai

See Applications / Homology Modeling.

- 763-772 **Development of quantitative structure–activity relationships for explanatory modeling of fast reacting (meth)acrylate monomers bearing novel functionality**, Jason A. Morrill [William Jewell College], Joedd H. Biggs, Christopher N. Bowman, Jeffrey W. Stansbury

See Methodology / QSAR.

Journal of Computational Chemistry, 32(3), February, 2011.

- 375–385 **Molecular dynamics simulations of aqueous ions at the liquid–vapor interface accelerated using graphics processors**, Brad A. Bauer, Joseph E. Davis, Michela Taufer [University of Delaware] and Sandeep Patel

See Methodology / Molecular Dynamics.

- 386–395 **Performance of 3D-space-based atoms-in-molecules methods for electronic delocalization aromaticity indices**, Wouter Heyndrickx, Pedro Salvador [University of Girona], Patrick Bultinck, Miquel Solà and Eduard Matito

Several definitions of an atom in a molecule (AIM) in three-dimensional (3D) space, including both fuzzy and disjoint domains, are used to calculate electron sharing indices (ESI) and related electronic aromaticity measures, namely, I_{ring} and multicenter indices (MCI), for a wide set of cyclic planar aromatic and nonaromatic molecules of different ring size.

- 396–405 **Rapid sampling of all-atom peptides using a library-based polymer-growth approach**, Artem B. Mamonov, Xin Zhang and Daniel M. Zuckerman [University of Pittsburgh]

We adapted existing polymer growth strategies for equilibrium sampling of peptides described by modern atomistic forcefields with a simple uniform dielectric solvent. The main novel feature of our approach is the use of precalculated statistical libraries of molecular fragments.

- 406–415 **Density functional theory study of a molecular allosteric switch for 2,2'-bipyridyl-3,3'-15-crown-5**, Yuan Miao, Xueye Wang [Xiangtan University], Xin Jin, Ling Yi and Cuihuan Ren

A classical model of “molecular machine,” which acts as an ON–OFF switch for 2,2'-bipyridyl-3,3'-15-crown-5 (L), has been theoretically studied.

- 416–428 **Interaction identification of Zif268 and TATA_{ZF} proteins with GC-/AT-rich DNA sequence: A theoretical study**, Bo Yang, Yanyan Zhu, Yan Wang and Guangju Chen [Beijing Normal University]

See Applications / Nucleic Acids.

- 429–438 **Density functional theory investigation of Cu(I)- and Cu(II)-curcumin complexes**, Matthew A. Addicoat [Australian National University], Gregory F. Metha and Tak W. Kee

Density functional theory is used to obtain the lowest energy geometries of bis-aqua curcumin complexes and bis-curcumin complexes of Cu(I) and Cu(II). Three conformations of curcumin, obtained by rotation of the substituted aromatic groups, were considered in each case.

- 439–452 **Nucleic acid sequence design via efficient ensemble defect optimization**, Joseph N. Zadeh, Brian R. Wolfe and Niles A. Pierce [California Institute of Technology]

See Applications / Nucleic Acids.

- 453–462 **The quest for the best nonpolarizable water model from the adaptive force matching method**, Omololu Akin-Ojo and Feng Wang [Boston University]

The recently introduced adaptive force matching (AFM) method is used to develop a significantly improved pair-wise nonpolarizable potential for water.

- 463–482 **Discovery of new β -D-galactosidase inhibitors via pharmacophore modeling and QSAR analysis followed by in silico screening**, Ahmed Mutanabbi Abdula, Reema Abu Khalaf, Mohammad S. Mubarak and Mutasem O. Taha [University of Jordan]

See Applications / Medicinal Chemistry and Drug Design.

- 483–496 **Effect of ligand binding on the intraminimum dynamics of proteins**, Burak Alakent [Bogazici University], Sena Baskan and Pemra Doruker

See Applications / Ligand Binding.

- 497–512 **Large-scale, long-term nonadiabatic electron molecular dynamics for describing material properties and phenomena in extreme environments**, Andres Jaramillo-Botero [California Institute of Technology], Julius Su, An Qi and William A. Goddard III

We describe the first principle-based electron force field (eFF) methodology for modeling the simultaneous dynamics of electrons and nuclei (eMD) evolving nonadiabatically under transient extreme conditions.

- 513–524 **Quality of random number generators significantly affects results of Monte Carlo simulations for organic and biological systems**, Timothy H. Click, Aibing Liu and George A. Kaminski [Worcester Polytechnic Institute]

See Methodology / Monte Carlo.

- 525–535 **Intramolecular interactions of L-phenylalanine: Valence ionization spectra and orbital momentum distributions of its fragment molecules**, Aravindhan Ganesan, Feng Wang [Swinburne University of Technology] and Chantal Falzon

See Methodology / QM and QM/MM.

- 536–544 **CABS-NMR—De novo tool for rapid global fold determination from chemical shifts, residual dipolar couplings and sparse methyl-methyl noes**, Dorota Latek [University of Warsaw] and Andrzej Kolinski

Recent development of nuclear magnetic resonance (NMR) techniques provided new types of structural restraints that can be successfully used in fast and low-cost global protein fold determination. Here, we present CABS-NMR, an efficient protein modeling tool, which takes advantage of such structural restraints.

Journal of Computational Chemistry, 32(4), March, 2011.

- 555-567 **Artificial neural network-based drug design for diabetes mellitus using flavonoids**, Jagdish C. Patra [Nanyang Technological University] and Boon H. Chua

See Applications / QSAR.

- 568-581 **VoteDock: Consensus docking method for prediction of protein–ligand interactions**, Dariusz Plewczynski [University of Warsaw], Michał Łażniewski, Marcin Von Grothuss, Leszek Rychlewski and Krzysztof Ginalski

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 582–599 **Communications on quantum similarity, part 3: A geometric-quantum similarity molecular superposition algorithm**, Ramon Carbó-Dorca [Universitat de Girona], Emili Besalú and Luz Dary Mercado

This work describes a new procedure to obtain optimal molecular superposition based on quantum similarity (QS): the geometric-quantum similarity molecular superposition (GQSMS) algorithm.

- 600–606 **Systematic benchmarking of large molecular dynamics simulations employing GROMACS on massive multiprocessing facilities**, Christian C. Gruber and Jürgen Pleiss [University of Stuttgart]

See Methodology / Molecular Dynamics.

- 607–619 **A simulation strategy for the atomistic modeling of flexible molecules covalently tethered to rigid surfaces: Application to peptides**, David Curcó [Universitat de Barcelona], David Zanuy, Ruth Nussinov and Carlos Alemán

See Methodology / Ligand Docking.

- 620–638 **Structural, electronic, and magnetoresponsive properties of triangular lanthanide clusters and their free-standing nitrides**, Athanassios C. Tsipis [University of Ioannina] and Alexandros V. Stalikas

The molecular and electronic structures, stabilities, bonding features, and magnetoresponsive properties of three-membered $[\text{c-Ln}_3]^{+/0/-}$ ($\text{Ln} = \text{La, Ce, Pr, Nd, Gd, Lu}$) and heterocyclic six-membered $[\text{c-Ln}_3\text{E}_3]^q$ ($\text{Ln} = \text{La, Ce, Pr, Nd, Gd, Lu}$; $\text{E} = \text{C, N}$; $q = 0 \text{ or } 1$) rings have been investigated by means of electronic structure calculation methods at the DFT level.

- 639–657 **Rapid estimation of activation enthalpies for cytochrome-P450-mediated hydroxylations**, Arthur N. Mayeno [Colorado State University], Jonathan L. Robinson and Brad Reisfeld

See Applications / Enzyme Catalysis.

- 658–667 **Thermochemical stabilities, electronic structures, and optical properties of $\text{C}_{56}\text{X}_{10}$ ($\text{X} = \text{H, F, and Cl}$) fullerene compounds**, Shu-Wei Tang, Jing-Dong Feng, Yong-Qing Qiu, Hao Sun, Feng-Di Wang, Zhong-Min Su, Ying-Fei Chang [Northeast Normal University] and Rong-Shun Wang

Stimulated by the recent isolation and characterization of $\text{C}_{56}\text{Cl}_{10}$ chlorofullerene (Tan et al., J Am Chem Soc 2008, 130, 15240), we perform a systematic study on the geometrical structures, thermochemistry, and electronic and optical properties of $\text{C}_{56}\text{X}_{10}$ ($\text{X} = \text{H, F, and Cl}$) on the basis of density functional theory (DFT).

- 668–674 **A TD-DFT study on the cyanide-chemosensing mechanism of 8-formyl-7-hydroxycoumarin**, Guang-Yue Li, Guang-Jiu Zhao, Ke-Li Han [Chinese Academy of Sciences] and Guo-Zhong He

Proton transfer (PT) and excited-state PT process are proposed to account for the fluorescent sensing mechanism of a cyanide chemosensor, 8-formyl-7-hydroxycoumarin.

- 675–680 **Similarity analysis of DNA sequences based on the weighted pseudo-entropy**, Chun Li [Bohai University], Hong Ma, Yang Zhou, Xiaolei Wang and Xiaoqi Zheng

A DNA primary sequence is a string consisting of letters on an alphabet $\Omega = \{a, c, g, t\}$. Based on all of the 2-combinations of the set Ω , here the repetition is allowed, we transform a DNA primary sequence into a special sequence over a set with cardinality 10.

- 681–688 **Steric effects on alkyl cation affinities of main group-element hydrides**, Juan M. Ruiz, R. Joshua Mulder, Célia Fonseca Guerra and F. Matthias Bickelhaupt [Scheikundig Laboratorium der Vrije Universiteit]

We have carried out an extensive exploration of gas-phase alkyl cation affinities (ACA) of archetypal anionic and neutral bases across the periodic system using zeroth order regular approximation-relativistic density functional theory at BP86/QZ4P//BP86/TZ2P.

- 689–695 **Extremely localized nonorthogonal orbitals by the pairing theorem**, T. Zoboki and I. Mayer [Hungarian Academy of Sciences]

Using the concepts of Löwdin pairing theorem, a method is developed to calculate extremely localized, but nonorthogonal, sets of molecular orbitals and their strictly localized counterparts.

- 696–708 **Generation of Kekulé valence structures and the corresponding valence bond wave function**, Zahid Rashid [Utrecht University] and Joop H. van Lenthe

A new scheme, called “list of nonredundant bonds”, is presented to record the number of bonds and their positions for the atoms involved in Kekulé valence structures of (poly)cyclic conjugated systems.

- 709–717 **Reliable protein structure refinement using a physical energy function**, Matthew S. Lin and Teresa Head-Gordon [UCSF/UCB Joint Graduate Group in Bioengineering]

In this work, we couple protein–solvent energy function with our global optimization method stochastic perturbation with soft constraints and use them to refine a collection of template models from submitted predictions to recent Critical Assessment of Techniques for Protein Structure Prediction blind prediction contests.

- 718–729 **Ab initio molecular geometry and anharmonic vibrational spectra of thiourea and thiourea-d₄**, Andrzej T. Kowal [Wrocław University of Technology]

Potential energy surface (PES) of thiourea, $\text{SC}(\text{NH}_2)_2$, has been searched for stable conformers under C_1 , C_s , C_2 , and C_{2v} symmetry constraints by post-Hartree–Fock ab initio methods with electron correlation level varying from second-order Møller–Plesset perturbation theory (MP2) to quadratic configuration interaction with single and double excitations (QCISD) and basis sets of double- and triple-zeta quality within 6-31+G(d,p) to aug-cc-pVTZ range.

- 730–736 **Computational study of static first hyperpolarizability of donor–acceptor substituted (E)-benzaldehyde phenylhydrazone**, Shih-I Lu [Soochow University]

Various hybrid functionals (B3LYP, B97-2, PBE0, BMK, BH&HLYP, CAM-B3LYP, and LC- ω PBE) implemented in density functional theory were applied to give estimate of static first hyperpolarizability (β_0) of (E)-benzaldehyde phenylhydrazone designated as (E)-BPH.

- 737-741 **Transport properties of graphene nanoribbon-based molecular devices**, Zongling Ding, Jun Jiang, Huaizhong Xing, Haibo Shu, Ruibin Dong, Xiaoshuang Chen [Chinese Academy of Sciences] and Wei Lu

The electronic and transport properties of an edge-modified prototype graphene nanoribbon (GNR) slice are investigated using density functional theory and Green's function theory.

Journal of Molecular Modeling, 17 (1), January, 2011.

- 1-8 **3D-QSAR studies on caspase-mediated apoptosis activity of phenolic analogues**, Yuanqiang Wang, Heng Zhang, Yong Lin, Qi Zhao and Hui Liu, Zhihua Lin [Chongqing University of Technology]

See Applications / QSAR.

- 9-19 **Anthranilate derivatives as TACE inhibitors: Docking based CoMFA and CoMSIA analyses**, Malkeet Singh Bahia, Shravan Kumar Gunda, Shwetha Reddy Gade, Saikh Mahmood and Ravikumar Muttineni, Om Silakari [Punjabi University]

See Applications / QSAR.

- 21-26 **A computational study of the mechanism of the unimolecular elimination of α,β -unsaturated aldehydes in the gas phase**, Valentina Erastova, Jesús Rodríguez-Otero [Universidade de Santiago de Compostela], Enrique M. Cabaleiro-Lago and Ángeles Peña-Gallego

The mechanism for the decarbonylation of (E)-2-butenal and (E)-2-methyl-3-phenyl-2-propenal was studied with different levels of ab initio and DFT methods.

- 27-36 **A leucine-rich repeat assembly approach for homology modeling of the human TLR5-10 and mouse TLR11-13 ectodomains**, Tiandi Wei, Jing Gong [Ludwig-Maximilians-Universität München], Shaila C. Rössle, Ferdinand Jamitzky and Wolfgang M. Heckl, et al.

See Applications / Homology Modeling.

- 37-48 **Structure and dynamics of human vimentin intermediate filament dimer and tetramer in explicit and implicit solvent models**, Zhao Qin and Markus J. Buehler [Massachusetts Institute of Technology]

See Applications / Protein Dynamics.

- 49-58 **Molecular modeling of 4-methylphthalonitrile for dye sensitized solar cells using quantum chemical calculations**, Palanivel Senthilkumar [Periyar University] and Ponnusamy Munusamy Anbarasan

The geometries, electronic structures, polarizabilities, and hyperpolarizabilities of organic dye sensitizer 4-Methylphthalonitrile was studied based on Hartree-Fock (HF) and density functional theory (DFT) using the hybrid functional B3LYP. Ultraviolet-visible (UV-Vis) spectrum was investigated by time dependent-density functional theory (TD-DFT).

- 59-72 **Urocanic acid as an efficient hydroxyl radical scavenger: a quantum theoretical study**, Saumya Tiwari and Phool Chand Mishra [Banaras Hindu University]

The mechanisms of stepwise reactions of trans-UCA with up to four hydroxyl radicals were investigated.

- 73-79 **Atomistic modeling of apatite-collagen composites from molecular dynamics simulations extended to hyperspace**, Patrick Duchstein and Dirk Zahn [Max-Planck-Institut für Chemische Physik fester Stoffe]

See Applications / Protein Dynamics.

- 81-88 **Electropolymerization of 3',4'-disubstituted 2,2':5',2''-terthiophene derivatives. A theoretical and photovoltaic characterization**, Jorge H. Vélez [Pontificia Universidad Católica de Chile], Soledad Gutiérrez-Oliva, Fernando R. Díaz, Maria Angelica del Valle and Alejandro Toro-Labbé, et al.

In the present work a series of β -substituted thiophenes have been synthesized and their electrochemical behavior studied.

- 89-96 **Carbon doped boron phosphide nanotubes: A computational study**, Mahmoud Mirzaei [Islamic Azad University]

See Applications / Carbon Nanoparticles.

- 97-109 **Computational characterization of how the VX nerve agent binds human serum paraoxonase 1**, Steven Z. Fairchild [The MITRE Corporation], Matthew W. Peterson, Adel Hamza, Chang-Guo Zhan and Douglas M. Cerasoli, et al.

Human serum paraoxonase 1 (HuPON1) is an enzyme that can hydrolyze various chemical warfare nerve agents including VX. A previous study has suggested that increasing HuPON1's VX hydrolysis activity one to two orders of magnitude would make the enzyme an effective countermeasure for in vivo use against VX. This study helps facilitate further engineering of HuPON1 for enhanced VX-hydrolase activity by computationally characterizing HuPON1's tertiary structure and how HuPON1 binds VX.

- 111-124 **Equivalent potential of water for the electronic structure of glycine**, Min Peng and Haoping Zheng [Tongji University]

First-principles, all-electron, ab initio calculations have been performed to construct an equivalent potential of water for the electronic structure of glycine (Gly) in solution.

- 125-131 **Hydroxyl group as a substituent with varying electronic properties: Effect of strength of H-bonding on charge density changes in Ph-OH...F⁻ complexes**, Halina Szatyłowicz [Warsaw University of Technology], Tadeusz Marek Krygowski and Aneta Jezierska-Mazzarello

Due to gradual and controlled changes of interatomic distances between heavy atoms in OH...F⁻ of C₆H₅OH...F⁻ systems it was possible to study the electronic structure evolution. Computation at B3LYP/6-311+G(d,p) level of theory was performed for this purpose.

- 133-150 **Binding Selectivity of RecA to a single stranded DNA, a computational approach**, Claudio Carra [Universities Space Research Association, 2101 NASA Parkway] and Francis A. Cucinotta

See Applications / Nucleic Acids.

- 151-163 **Ligand-based and structure-based approaches in identifying ideal pharmacophore against c-Jun N-terminal kinase-3**, B. V. S. Suneel Kumar, Rohith Kotla, Revanth Buddiga, Jyoti Roy and Sardar Shamshair Singh, Muttineni Ravikumar [GVK Biosciences Private Limited], et al.

Structure and ligand based pharmacophore modeling and docking studies carried out using diversified set of c-Jun N-terminal kinase-3 (JNK3) inhibitors are presented in this paper.

- 165-171 **Experimental and theoretical investigations on the structure-properties interrelationship of the gadolinium-vanadate-germanate glasses**, Simona Rada [Technical University of Cluj-Napoca], Ramona Chelcea and Eugen Culea

Glasses in the system $x\text{Gd}_2\text{O}_3 \cdot (100-x)[\text{GeO}_2 \cdot \text{V}_2\text{O}_5]$ with $0 \leq x \leq 20$ mol% have been prepared from the melt quenching method. In this paper, we investigated changes in germanium coordination number in gadolinium-vanadate-germanate glasses through molar volume analysis, measurements of densities, investigations of FTIR and UV-VIS spectroscopy, calculations of density functional theory (DFT).

- 173-179 **Optimal molecular structures of prion AGAAAAGA amyloid fibrils formatted by simulated annealing**, Jiapu Zhang [The University of Melbourne]

See Methodology / Homology Modeling.

- 181-200 **Conformational analysis of piperazine and piperidine analogs of GBR 12909: stochastic approach to evaluating the effects of force fields and solvent**, Deepangi Pandit, William Roosma, Milind Misra, Kathleen M. Gilbert and William J. Skawinski, Carol A. Venanzi. [New Jersey Institute of Technology]

Analogues of the flexible dopamine reuptake inhibitor, GBR 12909 (**1**), may have potential utility in the treatment of cocaine abuse. As a first step in the 3D-QSAR modeling of the dopamine transporter (DAT)/serotonin transporter (SERT) selectivity of these compounds, we carried out conformational analyses of two analogues of **1**: a piperazine (**2**) and a related piperidine (**3**).

Journal of Molecular Modeling, 17 (2), February, 2011.

- 209-218 **3D QSAR pharmacophore model based on diverse IKK β inhibitors**, Shanthi Nagarajan, Asif Ahmed, Hyunah Choo, Yong Seo Cho and Kwang-Seok Oh, Ae Nim Pae [Korea Institute of Science and Technology]

See Applications / QSAR.

- 219-226 **Homology modeling, molecular dynamic simulation and docking studies of cyclin dependent kinase 1**, Lei Zhang, Huawei Zhu, Qiang Wang, Hao Fang and Wenfang Xu, Minyong Li. [Shandong University]

See Applications / Homology Modeling.

- 227-234 **A force field for dynamic Cu-BTC metal-organic framework**, Lei Zhao, Qingyuan Yang, Qintian Ma, Chongli Zhong [Beijing University of Chemical Technology] and Jianguo Mi, et al.

A new force field that can describe the flexibility of Cu-BTC metal-organic framework (MOF) was developed in this work.

- 235-242 **Density functional theory study on $(\text{LiNH}_2)_n$ ($n = 1-5$) clusters**, Su-Qin Zhou, Su-Min Zhou, Tao Hu and Xue-Hai Ju [Nanjing University of Science and Technology]

Geometrical structures and relative stabilities of $(\text{LiNH}_2)_n$ ($n = 1-5$) clusters were studied using density functional theory (DFT) at the B3LYP/6-31G* and B3LYP/6-31++G* levels.

- 243-249 **Interaction between alkaline earth cations and oxo-ligands. DFT study of the affinity of the Ca^{2+} cation for carbonyl ligands**, Leonardo Moreira da Costa, José Walkimar de Mesquita Carneiro [Universidade Federal Fluminense], Gilberto Alves Romeiro and Lilian Weitzel Coelho Paes

The affinity of the Ca^{2+} ion for a set of substituted carbonyl ligands was analyzed with both the DFT (B3LYP/6-31+G(d)) and semi-empirical (PM6) methods.

- 251-263 **Insight into residues involved in the structure and function of the breast cancer associated protein human gamma synuclein**, Panneerselvam Manivel, Jayaraman Muthukumaran, Muthu Kannan and Ramadas Krishna [Pondicherry University]

Aberrantly expressed human gamma synuclein (SNCG) interacts with BubR1 and heat shock protein 70 (Hsp70) in late stages of breast and ovarian cancer. The objectives of this study were to generate a three-dimensional model of SNCG and to identify the key residues involved in interaction with BubR1, ANK peptide and Hsp70.

- 265-273 **Virtual screening of specific chemical compounds by exploring E.coli NAD^+ -dependent DNA ligase as a target for antibacterial drug discovery**, Bashir Akhlaq Akhoun [Punjabi University, Patiala], Shishir K Gupta, Gagan Dhaliwal, Mugdha Srivastava and Shailendra K Gupta

See Applications / Nucleic Acids.

- 275-279 **The studies on the aromaticity of fullerenes and their holmium endohedral compounds**, Bisheng Tan, Rufang Peng [Southwest University of Science and Technology], Hongbo Li, Bing Wang and Bo Jin, et al.

Density functional theory BLYP/DNP was employed to optimize a series of fullerenes and their holmium endohedral compounds, including C_{20} , Ho@C_{20} , $\text{Ho}^{3+}\text{@C}_{20}$, C_{60} , Ho@C_{60} , $\text{Ho}^{3+}\text{@C}_{60}$, C_{70} , Ho@C_{70} , $\text{Ho}^{3+}\text{@C}_{70}$, C_{78} , Ho@C_{78} , $\text{Ho}^{3+}\text{@C}_{78}$, C_{82} , Ho@C_{82} and $\text{Ho}^{3+}\text{@C}_{82}$.

- 281-287 **Electronic properties of neuroleptics: ionization energies of benzodiazepines**, Salvatore Millefiori [Università di Catania] and Andrea Alparone

Vertical ionization energies (VIEs) of medazepam, nordazepam and their molecular subunits have been calculated using the electron propagator method in the P3/CEP-31G* approximation.

- 289-300 **The effect of calciums on molecular motions of proteinase K**, Shu-Qun Liu, Yan Tao, Zhao-Hui Meng, Yun-Xin Fu and Ke-Qin Zhang [Yunnan University]

See Applications / Enzyme Catalysis.

- 301-313 **Molecular modeling studies of Fatty acyl-CoA synthetase (FadD13) from Mycobacterium tuberculosis—a potential target for the development of antitubercular drugs**, Nidhi Jatana, Sarvesh Jangid, Garima Khare, Anil K. Tyagi and Narayanan Latha [Sri Venkateswara College, New Delhi]

See Applications / Homology Modeling.

- 315-324 **A physical model for PDZ-domain/peptide interactions**, Kristian Kaufmann, Nicole Shen, Laura Mizoue and Jens Meiler [Vanderbilt University]

The PDZ domain is an interaction motif that recognizes and binds the C-terminal peptides of target proteins. We present an optimized energy function to predict the binding free energy ($\Delta\Delta G$) of PDZ domain/peptide interactions computationally.

- 325-331 **Aqueous solubility of a diatomic molecule as a function of its size & electronegativity difference**, Kamal I. Al-Malah [University of Hail]

The aqueous solubility of a diatomic molecule as a function of its size & electronegativity difference is investigated. The electronegativity of a diatomic molecule will be calculated using five different electronegativity scales, namely, Pauling [1], Allred-Rochow [2], Mulliken [3, 4], Parr-Yang [5], and Sanderson [6, 7].

- 333-357 **The binding modes and binding affinities of artemisinin derivatives with Plasmodium falciparum Ca²⁺-ATPase (PfATP6)**, Pradeep Kumar Naik [Jaypee University of Information Technology], Mani Srivastava, Prasad Bajaj, Sankalp Jain and Abhishek Dubey, et al.

See Applications / Homology Modeling.

- 359-376 **QSAR, DFT and quantum chemical studies on the inhibition potentials of some carbozones for the corrosion of mild steel in HCl**, Nnabuk O. Eddy [Ahmadu Bello University] and Benedict I. Ita

Experimental aspects of the inhibition of the corrosion of mild steel in HCl solutions by some carbozones were studied using gravimetric, thermometric and gasometric methods, while a theoretical study was carried out using density functional theory, a quantitative structure–activity relation, and quantum chemical principles.

- 377-381 **The effect of Li⁺ on GSK-3 inhibition: Molecular dynamics simulation**, Hao Sun, Yong-jun Jiang [Zhejiang University], Qing-sen Yu, Cheng-cai Luo and Jian-wei Zou

See Applications / Enzyme Catalysis.

- 383-389 **Docking study and binding free energy calculation of poly (ADP-ribose) polymerase inhibitors**, Kazuki Ohno, Takashi Mitsui, Yoshiaki Tanida, Azuma Matsuura and Hideaki Fujitani, Masaya Orita,[Astellas Pharma Inc.] et al.

See Applications / Free Energy Calculations.

- 391-399 **Identification of folding preferences of cleavage junctions of HIV-1 precursor proteins for regulation of cleavability**, Hirotaka Ode [National Institute of Infectious Diseases, 4-7-1 Gakuen], Masaru Yokoyama, Tadahito Kanda and Hironori Sato

See Applications / Protein Folding.

- 401-413 **Analysis of structural water and CH $\cdots\pi$ interactions in HIV-1 protease and PTP1B complexes using a hydrogen bond prediction tool, HBPredicT**, Joshy P. Yesudas, Fareed Bhasha Sayyed and Cherumuttathu H. Suresh [National Institute for Interdisciplinary Science and Technology (CSIR)]

A hydrogen bond prediction tool HBPredicT is developed for detecting structural water molecules and CH $\cdots\pi$ interactions in PDB files of protein-ligand complexes.

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About 100 Papers from 30 Journals are cited.

1	APPLICATIONS (70)	Page 2		
1.1	Small Molecules (17)			
	Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 5
	QSAR	Page 5		
1.2	Biopolymers (53)			
	Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 13
	Protein Structure Prediction	Page 7	Enzyme Catalysis	Page 14
	Comparative or Homology Modeling	Page 7	Protein-Protein Interactions	Page 15
	Protein Dynamics	Page 9	Membrane Proteins	Page 15
	Free Energy Calculations	Page 11	Nucleic Acids	Page 18
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 19		
2	METHODOLOGY (27)	Page 20		
	QSAR	Page 20	Free Energy Perturbations	Page 22
	Potentials and Parameters	Page 21	QM & QM/MM	Page 23
	Molecular Dynamics	Page 21	Ligand Docking	Page 25
	Monte Carlo	Page 22		
3	JOURNAL REVIEWS (4)	Page 27		
	Journal of Computational Chemistry, 35 (5), April, 2011.			
	Journal of Computational Chemistry, 35 (6), April, 2011.			
	Journal of Molecular Modeling, 17 (3), March, 2010.			
	Molecular Simulation, 37(3), 2011.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 36		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Synthesis, biological evaluation and 3D-QSAR studies of 3-keto salicylic acid chalcones and related amides as novel HIV-1 integrase inhibitors

Horrick Sharma, Shivaputra Patil, Tino W. Sanchez, Nouri Neamati, Raymond F. Schinazi, John K. Buolamwini
[University of Tennessee Health Science Center]

Bioorg. and Med.Chem., **19**, 2030-2045, 2011.

HIV-1 integrase is one of the three most important enzymes required for viral replication and is therefore an attractive target for anti retroviral therapy. We herein report the design and synthesis of 3-keto salicylic acid chalcone derivatives as novel HIV-1 integrase inhibitors. The most active compound, 5-bromo-2-hydroxy-3-[3-(2,3,6-trichlorophenyl)acryloyl]benzoic acid (**25**) was selectively active against integrase strand transfer, with an IC_{50} of 3.7 μ M. This model predicted all the ten compounds of the test set within 0.56 log units of the actual pIC_{50} values; and can be used to guide the rational design of more potent novel 3-keto salicylic acid integrase inhibitors.

Synthesis, stereochemistry, antimicrobial evaluation and QSAR studies of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones

S. Umamatheswari, B. Balaji, M. Ramanathan, S. Kabilan

Europ. Biophys. Jou., **46**, 1415-1424, 2011.

A series of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones (**11–27**) were synthesized and characterized for evaluation of potential antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Bacillus subtilis* and *Klebsiella pneumonia* and antifungal activity against *Cryptococcus neoformans*, *Candida albicans*, *Rhizopus sp.*, *Aspergillus niger* and *Aspergillus flavus* were evaluated. Further, the results of QSAR studies of these synthesized compounds indicated the importance of weakly polar component of surface area, hydrophobicity and ionization potential parameters in defining their antimicrobial activity.



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Medicinal Chemistry and Drug Design (Cont'd)

Computational simulations of structural role of the active-site W374C mutation of acetyl-coenzyme-A carboxylase: Multi-drug resistance mechanism

Xiao-Lei Zhu, Wen-Chao Yang, Ning-Xi Yu, Sheng-Gang Yang and Guang-Fu Yang [Central China Normal University]

J. Mol.Mod., **17**, 415-422, 2011.

Herbicides targeting grass plastidic acetyl-CoA carboxylase (ACCase, EC 6.4.1.2) are selectively effective against graminicides. Recently, the active-site W374C mutation was found to confer multi-drug resistance toward haloxyfop (HF), fenoxaprop (FR), Diclofop (DF), and clodinafop (CF) in *A. myosuroides*. In order to uncover the resistance mechanism due to W374C mutation, the binding of above-mentioned four herbicides to both wild-type and the mutant-type ACCase was investigated in the current work by molecular docking and molecular dynamics (MD) simulations.

Molecular Docking and Pharmacophore Filtering in the Discovery of Dual-Inhibitors for Human Leukotriene A4 Hydrolase and Leukotriene C4 Synthase

Sundarapandian Thangapandian, Shalini John, Sugunadevi Sakthiah, and Keun Woo Lee [Gyeongsang National University]

J.Chem. Infor. and Mod. **51**, 1759–1771, 2011.

Combination of drugs for multiple targets has been a standard treatment in treating various diseases. A single chemical entity that acts upon multiple targets is emerging nowadays because of their predictable pharmacokinetic and pharmacodynamic properties. We have employed a computer-aided methodology combining molecular docking and pharmacophore filtering to identify chemical compounds that can simultaneously inhibit the human leukotriene hydrolase (hLTA4H) and the human leukotriene C4 synthase (hLTC4S) enzymes.

Computational Insight into Small Molecule Inhibition of Cyclophilins

Somisetti V. Sambasivarao and Orlando Acevedo [Auburn University]

J.Chem. Infor. and Mod. **51**, 475–482, 2011.

Cyclophilins (Cyp) are a family of cellular enzymes possessing peptidyl-prolyl isomerase activity, which catalyze the cis–trans interconversion of proline-containing peptide bonds. The two most abundant family members, CypA and CypB, have been identified as valid drug targets for a wide range of diseases, including HCV, HIV, and multiple cancers. Monte Carlo statistical sampling coupled to free energy perturbation theory (MC/FEP) calculations have been carried out to elucidate the origin of the experimentally observed nM inhibition of CypA by acylurea-based derivatives and the >200-fold in vitro selectivity between CypA and CypB from aryl 1-indanylketo-based μM inhibitors.

A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity

Cristian Obiol-Pardo, Julio Gomis-Tena, Ferran Sanz, Javier Saiz, and Manuel Pastor [Universitat Pompeu Fabra]

J.Chem. Infor. and Mod. **51**, 483–492, 2011.

The preclinical assessment of drug-induced ventricular arrhythmia, a major concern for regulators, is typically based on experimental or computational models focused on the potassium channel hERG (human ether-a-go-go-related gene, $K_v11.1$). We introduce a multiscale simulation system aiming to produce a better cardiotoxicity assessment. At the molecular scale, the proposed system uses a combination of docking simulations on two potassium channels, hERG and KCNQ1, plus three-dimensional quantitative structure–activity relationship modeling for predicting how the tested compound will block the potassium currents IK_r and IK_s .

Medicinal Chemistry and Drug Design (Cont'd)

Interaction of clozapine and its nitrenium ion with rat D2 dopamine receptors: in vitro binding and computational study

Sébastien Dilly and Jean-François Liégeois [University of Liège]

J. Comp. Aided Mol. Des. **25**, 163-169, 2011.

The interaction of diazepine analogues like clozapine or olanzapine with D2 receptor was greatly affected by a mixture of HRP/H₂O₂ known to induce the formation of nitrenium ion. Unlike diazepine derivatives, the oxidative mixture had low impact on the affinity of oxa- and thiazepine derivatives such as loxapine, clothiapine or JL13 for the D2 receptor. Molecular docking simulations revealed a huge difference between the mode of interaction of clozapine nitrenium ion and the parent drug.

Prediction of Solubility Parameters and Miscibility of Pharmaceutical Compounds by Molecular Dynamics Simulations

Jasmine Gupta [University of the Sciences in Philadelphia], Cletus Nunes, Shyam Vyas, and Sriramakamal Jonnalagadda

J. Phys. Chem. B., **115**, 2014–2023, 2011.

The objectives of this study were (i) to develop a computational model based on molecular dynamics technique to predict the miscibility of indomethacin in carriers (polyethylene oxide, glucose, and sucrose) and (ii) to experimentally verify the in silico predictions by characterizing the drug-carrier mixtures using thermoanalytical techniques. Molecular dynamics (MD) simulations were performed using the COMPASS force field, and the cohesive energy density and the solubility parameters were determined for the model compounds.

Structure-based and ligand-based drug design for microsomal prostaglandin E synthase-1 inhibitors

Chia-Ling Li [China Medical University Hospital]; Tung-Ti Chang; Mao-Feng Sun; Hsin-Yi Chen; Fuu-Jen Tsai; Mark Fisher; Calvin Yu-Chian Chen; Chun-Lin Lee; Wen-Chang Fang; Yung-Hao Wong

Molecular Simulation, **37**, 226 – 236, 2011.

Microsomal prostaglandin E synthase-1 (mPGES-1) has been regarded as an attractive drug for inflammation-related diseases. In search of new mPGES-1 inhibitors, we performed virtual screening using our traditional Chinese medicine and natural products database (<http://tcm.cmu.edu.tw/>) and constructed comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) using a training set of 30 experimentally tested mPGES-1 inhibitors.

Molecular dynamics analysis of potent inhibitors of M2 proton channel against H1N1 swine influenza virus

Chia-Yu Lai [China Medical University]; Tung-Ti Chang; Mao-Feng Sun; Hsin-Yi Chen; Fuu-Jen Tsai; Jaung-Geng Lin; Calvin Yu-Chian Chen

Molecular Simulation, **37**, 250 – 256, 2011.

The recent H1N1 (swine) influenza pandemic highlighted the urgent need of having effective anti-viral strategies. In order to identify novel M2 inhibitors, we have performed molecular docking using a traditional Chinese medicine database (<http://tcm.cmu.edu.tw/index.php>). Docking and subsequent de novo designs gave 10 derivatives that have much better docking results than the control. Docking and subsequent de novo designs gave 10 derivatives that have much better docking results than the control.

Quantitative Structure-Activity Relations

Discovery of new β -D-glucosidase inhibitors via pharmacophore modeling and QSAR analysis followed by in silico screening

Reema Abu Khalaf, Ahmed Mutanabbi Abdula, Mohammad S. Mubarak and Mutasem O. Taha [University of Jordan]

J. Mol.Mod., **17**, 443-464, 2011.

Glycosidases, including β -D-glucosidase, are involved in a variety of metabolic disorders such as diabetes, viral or bacterial infections and cancer. Accordingly, we were prompted to find new β -D-glucosidase inhibitors. Towards this end we scanned the pharmacophoric space of this enzyme using a set of 41 known inhibitors. Genetic algorithm and multiple linear regression analyses were employed to select an optimal combination of pharmacophoric models and physicochemical descriptors to yield self-consistent and predictive quantitative structure-activity relationship (QSAR).

Molecular dynamics studies of the 3D structure and planar ligand binding of a quadruplex dimer

Ming-Hui Li, Quan Luo, Xiang-Gui Xue and Ze-Sheng Li [Jilin University]

J. Mol.Mod., **17**, 515-526, 2011.

G-rich sequences can fold into a four-stranded structure called a G-quadruplex, and sequences with short loops are able to aggregate to form stable quadruplex multimers. Few studies have characterized the properties of this variety of quadruplex multimers. Using molecular modeling and molecular dynamics simulations, the present study investigated a dimeric G-quadruplex structure formed from a simple sequence of d(GGGTGGGTGGGTGGGT) (G1), and its interactions with a planar ligand of a perylene derivative (Tel03).

Structure-activity relationships of diphenyl-ether as protoporphyrinogen oxidase inhibitors: insights from computational simulations

Ge-Fei Hao, Ying Tan, Ning-Xi Yu and Guang-Fu Yang [Central China Normal University]

J. Comp. Aided Mol. Des. **25**, 213-222, 2011.

Protoporphyrinogen oxidase (PPO, EC 1.3.3.4), which has been identified as a significant target for a great family of herbicides with diverse chemical structures, is the last common enzyme responsible for the seventh step in the biosynthetic pathway to heme and chlorophyll. Herein, molecular dynamics simulations, approximate free energy calculations and hydrogen bond energy calculations were integrated together to uncover the structure-activity relationships of this type of PPO inhibitors.

Carbon Nanoparticles

Atomistic Molecular Dynamics Simulations of Peptide Amphiphile Self-Assembly into Cylindrical Nanofibers

One-Sun Lee, Samuel I. Stupp, and George C. Schatz [Northwestern University]

J. Am. Chem. Soc., **133**, 3677-3683, 2011.

Relaxation of a self-assembled structure of 144 peptide amphiphile (PA) molecules into cylindrical nanofibers is studied using atomistic molecular dynamics simulations including explicit water with physiological ion concentration. The PA for these studies includes a hydrophobic alkyl chain that is attached to the N-terminus of the sequence SLSLAAAEIKVAV. The self-assembly is initiated with PA molecules in a roughly cylindrical configuration, as suggested from previous experimental and theoretical investigations, and the cylindrical configuration that results is found to be stable during 40 ns simulations.

Carbon Nanoparticles (Cont'd)

A computational study of atomic oxygen-doped silicon carbide nanotubes

Maryam Mirzaei and Mahmoud Mirzaei [Islamic Azad University]

J. Mol.Mod., **17**, 527-531, 2011.

We investigated the properties of atomic oxygen-doped (O-doped) models of representative (6,0) and (4,4) silicon carbide nanotubes (SiCNTs) by density functional theory (DFT) calculations of isotropic and anisotropic chemical shielding (CS) parameters of Si-29, O-17 and C-13 atoms for the optimized structures. The calculated parameters indicated the effects of O-doping on the electronic environments of the first neighboring atoms of the doped sites.

Characterisation, applicability and defect analysis for tiles nanostructure of quantum dot cellular automata

Kunal Das [West Bengal University of Technology]; Debashis De

Molecular Simulation, **37**, 210 – 225, 2011.

Quantum dot cellular automata (QCA) is an emerging technology for nanoscale computing. In this paper, our contribution is to enhance the applicability of 3×3 tile nanostructure in QCA. We introduced few novel 3×3 active-type tiles, namely triple fan-output tiles or butterfly tile, five-input majority voter (MV) and fault-tolerant 3×3 tile-coupled majority-minority voter. We also explored the cascading effect on 3×3 tile. Triple fan-out tile is applicable to drive three outputs simultaneously.

1.2. Biopolymers

Bioinformatics and Cheminformatics

R/mpMap: a computational platform for the genetic analysis of multiparent recombinant inbred lines

B. Emma Huang [CSIRO, St Lucia] and Andrew W. George

Bioinformatics. **27**, 727-729, 2011.

Multiparent crosses of recombinant inbred lines provide opportunity to map markers and quantitative trait loci (QTL) with much greater resolution than is possible in biparental crosses. R/mpMap provides a flexible and extensible environment, which interfaces easily with other packages to satisfy this demand. Functions in the package encompass simulation, marker map construction, haplotype reconstruction and QTL mapping. We demonstrate the easy-to-use features of mpMap through a simulated data example.

Quantitative trait prediction based on genetic marker-array data, a simulation study

Wai-ki Yip [Harvard School of Public Health] and Christoph Lange

Bioinformatics. **27**, 745-748, 2011.

Using simulation studies for quantitative trait loci (QTL), we evaluate the prediction quality of regression models that include as covariates single-nucleotide polymorphism (SNP) genetic markers which did not achieve genome-wide significance in the original genome-wide association study, but were among the SNPs with the smallest P-value for the selected association test. We compare the results of such regression models to the standard approach which is to include only SNPs that achieve genome-wide significance.

Bioinformatics and Cheminformatics (Cont'd)

Computerized evaluation of mean residence times in multicompartmental linear system and pharmacokinetics

J. M. Villalba, A. J. Barbero, R. Diaz-Sierra, E. Arribas, M. J. Garcia-Meseguer, F. Garcia-Sevilla, M. Garcia-Moreno, J. A. Vidal De Labra and R. Varon [Universidad de Castilla-La Mancha]

J. Comp. Chem. **32**, 915–931, 2011.

Deriving mean residence times (MRTs) is an important task both in pharmacokinetics and in multicompartmental linear systems. Taking as starting point the analysis of MRTs in open or closed (Garcia-Meseguer et al., *Bull Math Biol* 2003, 65, 279) multicompartmental linear systems, we implement a versatile software, using the Visual Basic 6.0 language for MS-Windows, that is easy to use and with a user-friendly format for the input of data and the output of results.

Protein Structure Prediction

Computational Protein Design and Large-Scale Assessment by I-TASSER Structure Assembly Simulations

Andrea Bazzoli, Andrea G.B. Tettamanzi, Yang Zhang [University of Michigan]

J. Molec. Bio. **407**, 43-48, 2011.

Protein design aims at designing new protein molecules of desired structure and functionality. We present a new protocol for protein design and validation. The sequence space is initially searched by Monte Carlo sampling guided by a public atomic potential, with candidate sequences selected by the clustering of sequence decoys. The designed sequences are then assessed by I-TASSER folding simulations, which generate full-length atomic structural models by the iterative assembly of threading fragments.

Comparative or Homology Modeling

Interaction of Diverse Voltage Sensor Homologs with Lipid Bilayers Revealed by Self-Assembly Simulations

Younes Mokrab, Mark S.P. Sansom [University of Oxford]

Biophysical Journal. **100**, 875-884, 2011.

Voltage sensors (VS) domains couple the activation of ion channels/enzymes to changes in membrane voltage. We used molecular dynamics simulations to examine interactions with lipids of several VS homologs. VSs in intact channels in the activated state are exposed to phospholipids, leading to a characteristic local distortion of the lipid bilayer which decreases its thickness by ~ 10 Å. This effect is mediated by a conserved hydrophilic stretch in the S4–S5 segment linking the VS and the pore domains, and may favor gating charges crossing the membrane.

Comparative or Homology Modeling (Cont'd)

Molecular modeling of lanthionine synthetase component C-like protein 2: a potential target for the discovery of novel type 2 diabetes prophylactics and therapeutics

Pinyi Lu, David R. Bevan, Stephanie N. Lewis, Raquel Hontecillas and Josep Bassaganya-Riera [Virginia Polytechnic Institute and State University]

J. Mol.Mod., **17**, 543-553, 2011.

The rates of type 2 diabetes (T2D) are rising to epidemic proportions in the US and worldwide. While current T2D medications are efficacious, significant side effects have limited their use and availability. Our laboratory has discovered that abscisic acid (ABA) exerts anti-diabetic effects, in part, by activating peroxisome proliferator-activated receptor γ (PPAR γ). The goal of this study was to determine whether LANCL2 is a molecular target of ABA and other PPAR γ agonists. To this end we performed homology modeling to construct a three-dimensional structure of LANCL2 using the crystal structure of LANCL1 as a template.

G Protein- and Agonist-Bound Serotonin 5-HT_{2A} Receptor Model Activated by Steered Molecular Dynamics Simulations

Vignir Isberg, Thomas Balle, Tommy Sander, Flemming Steen Jørgensen, and David E. Gloriam [University of Copenhagen]

J.Chem. Infor. and Mod. **51**, 315–325, 2011.

A 5-HT_{2A} receptor model was constructed by homology modeling based on the β_2 -adrenergic receptor and the G protein-bound opsin crystal structures. The 5-HT_{2A} receptor model was transferred into an active conformation by an agonist ligand and a G_{aq} peptide in four subsequent steered molecular dynamics (MD) simulations. The driving force for the transformation was the addition of several known intermolecular and receptor interhelical hydrogen bonds enforcing the necessary helical and rotameric movements. Subsequent MD simulations without constraints confirmed the stability of the activated receptor model as well as revealed new information about stabilizing residues and bonds.

Molecular Dynamics Simulations of CXCL-8 and Its Interactions with a Receptor Peptide, Heparin Fragments, and Sulfated Linked Cyclitols

Neha S. Gandhi and Ricardo L. Mancera [Curtin University]

J.Chem. Infor. and Mod. **51**, 335–358, 2011.

CXCL-8 (Interleukin 8) is a CXC chemokine with a central role in the human immune response. We have undertaken extensive in silico analyses to elucidate the interactions of CXCL-8 with its various binding partners, which are crucial for its biological function. Molecular dynamics simulations in aqueous solution of dimeric CXCL-8 have been performed with starting geometries from both X-ray and NMR structures showed shearing movements between the two antiparallel C-terminal helices.

Structural-dynamical investigation of the ZnuA histidine-rich loop: involvement in zinc management and transport

Mattia Falconi [University of Rome “Tor Vergata”], Francesco Oteri, Francesco Di Palma, Saurabh Pandey and Andrea Battistoni, et al.

J. Comp. Aided Mol. Des. **25**, 181-194, 2011.

Comparative homology modelling techniques have been used to model the protein ZnuA from *Salmonella enterica* serovar Typhimurium using the 3D structure of the homologous protein from *Escherichia coli*. These two-domain proteins bind one Zn²⁺ atom, with high affinity, in the inter-domain cleft and possess a histidine-rich loop in the N-terminal domain. Alternative structures of the ZnuA histidine-rich loop, never resolved by the X-ray diffraction method, have been modelled.

Comparative or Homology Modeling (Cont'd)

Structure-guided fragment-based in silico drug design of dengue protease inhibitors

Tim Knehans, Andreas Schüller, Danny N. Doan, Kassoum Nacro and Jeffrey Hill, Tanja Weil and Subhash G. Vasudevan [Duke-NUS Graduate Medical School]

J. Comp. Aided Mol. Des. **25**, 263-274, 2011.

An in silico fragment-based drug design approach was devised and applied towards the identification of small molecule inhibitors of the dengue virus (DENV) NS2B-NS3 protease. Currently, no DENV protease co-crystal structure with bound inhibitor and fully formed substrate binding site is available. Therefore a homology model of DENV NS2B-NS3 protease was generated employing a multiple template spatial restraints method and used for structure-based design. A library of molecular fragments was derived from the ZINC screening database with help of the retrosynthetic combinatorial analysis procedure (RECAP).

Protein Dynamics

3₁₀-Helix Conformation Facilitates the Transition of a Voltage Sensor S4 Segment toward the Down State

Christine S. Schwaiger, Pär Bjelkmar, Berk Hess, Erik Lindahl [Swedish e-Science Research Center]

Biophysical Journal. **100**, 1446-1454, 2011.

The activation of voltage-gated ion channels is controlled by the S4 helix, with arginines every third residue. The x-ray structures are believed to reflect an open-inactivated state, and models propose combinations of translation, rotation, and tilt to reach the resting state. Recently, experiments and simulations have independently observed occurrence of 3₁₀-helix in S4. This suggests S4 might make a transition from α - to 3₁₀-helix in the gating process. Here, we show 3₁₀-helix structure between Q1 and R3 in the S4 segment of a voltage sensor appears to facilitate the early stage of the motion toward a down state.

Resveratrol Inhibits the Formation of Multiple-Layered β -Sheet Oligomers of the Human Islet Amyloid Polypeptide Segment 22–27

Ping Jiang, Weifeng Li, Joan-Emma Shea, Yuguang Mu [Nanyang Technological University]

Biophysical Journal. **100**, 1550-1558, 2011.

The abnormal self-assembly of a number of proteins or peptides is a hallmark of >20 amyloidogenic diseases. In this article, we present extensive replica-exchange molecular dynamics simulations to study the early aggregation of the human islet amyloid polypeptide segment 22–27 in the presence and absence of the small-molecule inhibitor resveratrol. The simulations indicate that aggregation of these peptides was hindered by resveratrol via a mechanism of blocking the lateral growth of a single-layered β -sheet oligomer (rather than preventing growth by elongation along the fibril axis).

Molecular dynamics of ribosomal elongation factors G and Tu

Katarzyna Kulczycka, Maciej Długosz and Joanna Trylska [University of Warsaw]

Europ. Biophys. Jou., **40**, 289-303, 2011.

Translation on the ribosome is controlled by external factors. During polypeptide lengthening, elongation factors EF-Tu and EF-G consecutively interact with the bacterial ribosome. EF-Tu binds and delivers an aminoacyl-tRNA to the ribosomal A site and EF-G helps translocate the tRNAs between their binding sites after the peptide bond is formed. To characterize the internal motion of these two elongation factors, we used 25 ns long all-atom molecular dynamics simulations.

Protein Dynamics (Cont'd)

Metadynamics Study of a β -Hairpin Stability in Mixed Solvents

Giorgio Saladino, Stefano Pieraccini, Stefano Rendine, Teresa Recca, Pierangelo Francescato, Giovanna Speranza, and Maurizio Sironi [Universita' degli Studi di Milano]

J. Am. Chem. Soc., **133**, 2897–2903, 2011.

Understanding the molecular mechanisms that allow some organisms to survive in extremely harsh conditions is an important achievement. Here we describe a computational approach that, taking advantage of the recently developed metadynamics technique, allows one to fully describe the free energy surface of a small β -hairpin peptide and how it is affected by an osmoprotectant, glycine betaine and for comparison by urea, a common denaturant.

Mechanism of the Conformational Change of the F₁-ATPase β Subunit Revealed by Free Energy Simulations

Yuko Ito, Tomotaka Oroguchi, and Mitsunori Ikeguchi [Yokohama City University]

J. Am. Chem. Soc., **133**, 3372–3380, 2011.

F₁-ATPase is an ATP-driven rotary motor enzyme. The β subunit changes its conformation from an open to a closed form upon ATP binding. The motion in the β subunit is regarded as a major driving force for rotation of the central stalk. In this Article, we explore the conformational change of the β subunit using all-atom free energy simulations with explicit solvent and propose a detailed mechanism for the conformational change.

Efficient quantification of the importance of contacts for the dynamical stability of proteins

Kay Hamacher [TU Darmstadt]

J. Comp. Chem. **32**, 810–815, 2011.

Understanding the stability of the native state and the dynamics of a protein is of great importance for all areas of biomolecular design. Here, we use a recently suggested, information theoretical measure in biomolecular design — the Kullback–Leibler-divergence — to quantify and therefore rank residue–residue contacts within proteins according to their overall contribution to the molecular mechanics.

Molecular trigger for pre-transfer editing pathway in Valyl-tRNA synthetase: A molecular dynamics simulation study

Li Li, Long Yu and Qiang Huang [Fudan University]

J. Mol.Mod., **17**, 555–564, 2011.

Pre-transfer editing pathway in Valyl-tRNA synthetase (ValRS) is a very important process to maintain the high fidelity of protein synthesis. However, molecular basis for this pathway remains unclear. Here we employed MD simulation to study two complexes, ValRS·tRNA^{val}·Val-AMP and ValRS·tRNA^{val}·Thr-AMP, and compared their simulation trajectories, in order to understand how the pre-transfer editing pathway is triggered by the noncognate substrate Thr-AMP.

Improving the Wang–Landau algorithm for polymers and proteins

Adam D. Swetnam and Michael P. Allen [University of Warwick]

J. Comp. Chem. **32**, 816–821, 2011.

The 1/t Wang–Landau algorithm is tested on simple models of polymers and proteins. It is found that this method resolves the problem of the saturation of the error present in the original algorithm for lattice polymers. However, for lattice proteins, which have a rough energy landscape with an unknown energy minimum, it is found that the density of states does not converge in all runs. A new variant of the Wang–Landau algorithm that appears to solve this problem is described and tested. In the new variant, the optimum modification factor is calculated in the same straightforward way throughout the simulation.

Protein Dynamics (Cont'd)

Molecular jamming—The cystine slipknot mechanical clamp in all-atom simulations

Łukasz Peplowski [Nicolaus Copernicus University], Mateusz Sikora, Wiesław Nowak, and Marek Cieplak

Jou. Chem. Phys., **134**, 085102, 2011.

A recent survey of 17 134 proteins has identified a new class of proteins which are expected to yield stretching induced force peaks in the range of 1 nN. Such high force peaks should be due to forcing of a slip-loop through a cystine ring, i.e., by generating a cystine slipknot. The survey has been performed in a simple coarse grained model. Here, we perform all-atom steered molecular dynamics simulations on 15 cystine knot proteins and determine their resistance to stretching.

Modeling of the structure and interactions of the B. anthracis antitoxin, MoxX: deletion mutant studies highlight its modular structure and repressor function

Nikita Chopra, Shivangi Agarwal, Shashikala Verma, Sonika Bhatnagar and Rakesh Bhatnagar [Jawaharlal Nehru University]

*J. Comp. Aided Mol. Des.***25**, 275-291, 2011.

Our previous report on *Bacillus anthracis* toxin-antitoxin module (MoxXT) identified it to be a two component system wherein, PemK-like toxin (MoxT) functions as a ribonuclease (Agarwal S et al. JBC 285:7254–7270, 2010). The labile antitoxin (MoxX) can bind to/neutralize the action of the toxin and is also a DNA-binding protein mediating autoregulation. In this study, molecular modeling of MoxX in its biologically active dimeric form was done. It was found that it contains a conserved Ribbon-Helix-Helix (RHH) motif, consistent with its DNA-binding function.

Dynamic communication between androgen and coactivator: Mutually induced conformational perturbations in androgen receptor ligand-binding domain

Xue Xu, Wei Yang, Xia Wang, Yan Li, Yonghua Wang [Northwest A & F University] and Chunzhi Ai

Proteins: Stru. Fun. and Bioinfo. **79**, 1154–1171, 2011.

The transcriptional activity of androgen receptor (AR) is regulated by the sequential binding of various ligands (e.g., dihydrotestosterone, DHT) and coactivators (e.g., SRC/p160) to the AR ligand binding domain (LBD) (Askew et al., J Biol Chem 2007;282:25801–25816, Lee and Chang, Cell Mol Life Sci 2003;60:1613–1622). Thus, in this work, extensive explicit-solvent molecular dynamics (MD) simulations on four independent trajectories, that is, AR-apo (unbound), DHT·AR, AR·SRC, and DHT·AR·SRC, are performed to investigate the potential communications between the two events in the AR transcriptional process.

Free Energy Calculations

Electrostatic solvation free energy of amino acid side chain analogs: Implications for the validity of electrostatic linear response in water

Bin Lin and B. Montgomery Pettitt [Baylor College of Medicine]

J. Comp. Chem. **32**, 878–885, 2011.

Electrostatic free energies of solvation for 15 neutral amino acid side chain analogs are computed. We compare three methods of varying computational complexity and accuracy for three force fields: free energy simulations, Poisson-Boltzmann (PB), and linear response approximation (LRA) using AMBER, CHARMM, and OPLS-AA force fields. We find that deviations from simulation start at low charges for solutes.

Free Energy Calculations (Cont'd)

Multipole electrostatics in hydration free energy calculations

Yue Shi, Chuanjie Wu, Jay W. Ponder and Pengyu Ren [The University of Texas]

J. Comp. Chem. **32**, 967–977, 2011.

Hydration free energy (HFE) is generally used for evaluating molecular solubility, which is an important property for pharmaceutical and chemical engineering processes. Accurately predicting HFE is also recognized as one fundamental capability of molecular mechanics force field. Here, we present a systematic investigation on HFE calculations with AMOEBA polarizable force field at various parameterization and simulation conditions. The HFEs of seven small organic molecules have been obtained alchemically using the Bennett Acceptance Ratio method.

Protein inherent structures by different minimization strategies

Francesco Rao [University of Freiburg]

J. Comp. Chem. **32**, 1113–1116, 2011.

Network-based methods provide an accurate description of the free-energy landscape of peptides and proteins sampled by molecular dynamics simulations. To that end, it is necessary to group the individual snapshots in a meaningful way. The inherent structures (ISs) provide an appropriate discretization of the trajectory into microstates, avoiding problems that can arise in clustering algorithms that have been used previously. In this work, different minimization protocols to obtain the IS of a peptide are investigated on the basis of cut-based free-energy profiles.

A theoretical survey on the structures, energetics, and isomerization pathways of the B₅O radical

Chang-Bin Shao, Lin Jin and Yi-Hong Ding [Jilin University]

J. Comp. Chem. **32**, 771–777, 2011.

Pre-calculated libraries of molecular fragment configurations have previously been used as a basis for both equilibrium sampling (via library-based Monte Carlo) and for obtaining absolute free energies using a polymer-growth formalism. Here, we combine the two approaches to extend the size of systems for which free energies can be calculated. We study a series of all-atom poly-alanine systems in a simple dielectric solvent and find that precise free energies can be obtained rapidly.

Assessing the Performance of the MM/PBSA and MM/GBSA Methods. 1. The Accuracy of Binding Free Energy Calculations Based on Molecular Dynamics Simulations

Tingjun Hou, Junmei Wang, Youyong Li, and Wei Wang [University of California at San Diego]

J.Chem. Infor. and Mod. **51**, 69–82, 2011.

The Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) and the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) methods calculate binding free energies for macromolecules by combining molecular mechanics calculations and continuum solvation models. To systematically evaluate the performance of these methods, we report here an extensive study of 59 ligands interacting with six different proteins. First, we explored the effects of the length of the molecular dynamics (MD) simulation, ranging from 400 to 4800 ps, and the solute dielectric constant (1, 2, or 4) on the binding free energies predicted by MM/PBSA.

Free Energy Calculations (Cont'd)

Free energy of conformational transition paths in biomolecules: The string method and its application to myosin VI

Victor Ovchinnikov [Harvard University], Martin Karplus, and Eric Vanden-Eijnden

Jou. Chem. Phys., **134**, 085103, 2011.

A set of techniques developed under the umbrella of the string method is used in combination with all-atom molecular dynamics simulations to analyze the conformation change between the prepowerstroke (PPS) and rigor (R) structures of the converter domain of myosin VI. The challenges specific to the application of these techniques to such a large and complex biomolecule are addressed in detail. The methodology developed here is expected to be useful more generally in studies of conformational transitions in complex biomolecules.

Ligand Binding/Docking

Rapid evaluation of the binding energies in hydrogen-bonded amide-thymine and amide-uracil dimers in gas phase

Yang Li, Xiao-Nan Jiang and Chang-Sheng Wang [Liaoning Normal University]

J. Comp. Chem. **32**, 953–966, 2011.

The binding energies and the equilibrium hydrogen bond distances as well as the potential energy curves of 48 hydrogen-bonded amide-thymine and amide-uracil dimers are evaluated from the analytic potential energy function established in our lab recently. The calculation results show that the potential energy curves obtained from the analytic potential energy function are in good agreement with those obtained from MP2/6-311+G** calculations by including the BSSE correction.

Crystal molecular dynamics simulations to speed up MM/PB(GB)SA evaluation of binding free energies of di-mannose deoxy analogs with P51G-m4-Cyanovirin-N

Ivan I. Vorontsov and Osamu Miyashita [University of Arizona]

J. Comp. Chem. **32**, 1043–1053, 2011.

Complexes of two Cyanovirin-N (CVN) mutants, m4-CVN and P51G-m4-CVN, with deoxy di-mannose analogs were employed as models to generate conformational ensembles using explicit water Molecular Dynamics (MD) simulations in solution and in crystal environment. The results were utilized for evaluation of binding free energies with the molecular mechanics Poisson-Boltzmann (or Generalized Born) surface area, MM/PB(GB)SA, methods. The calculations provided the ranking of deoxy di-mannose ligands affinity in agreement with available qualitative experimental evidences.

Molecular Dynamics Simulations of a Binding Intermediate between FKBP12 and a High-Affinity Ligand

Lilian Olivieri and Fabrice Gardebien [Universite de la Reunion]

J. Chem. Theor. and Comp, **7**, 725–741, 2011.

We characterized a binding intermediate between the protein FKBP12 and one of its high-affinity ligands by means of molecular dynamics simulations. In such an intermediate, which is expected to form at the end-point of the bimolecular diffusional search, short-range interactions between the molecular partners may play a role in the specificity of recognition as well as in the association rate. Langevin dynamics simulations were carried out to generate the intermediate by applying an external biasing force to unbind the ligand from the protein.

Ligand Binding / Docking (Cont'd)

Computational Characterization of the Substrate-Binding Mode in Coproporphyrinogen III Oxidase

Pedro J. Silva and Maria Joao Ramos [Universidade do Porto]

J. Phys. Chem. B., **115**, 1903–1910, 2011.

Oxygen-dependent coproporphyrinogen III oxidase catalyzes the sequential decarboxylation of the propionate substituents present on the A and B rings of coproporphyrinogen III in the heme biosynthetic pathway. The molecular dynamics simulations described in this paper enabled the determination of a very promising substrate binding mode and the extensive characterization of the enzyme active site.

Enzyme Catalysis

The first branching point in porphyrin biosynthesis: A systematic docking, molecular dynamics and quantum mechanical/molecular mechanical study of substrate binding and mechanism of uroporphyrinogen-III decarboxylase

Eric A. C. Bushnell, Edwin Erdtman, Jorge Llano, Leif A. Eriksson and James W. Gauld [University of Windsor]

J. Comp. Chem. **32**, 822–834, 2011.

In humans, uroporphyrinogen decarboxylase is intimately involved in the synthesis of heme, where the decarboxylation of the uroporphyrinogen-III occurs in a single catalytic site. Several variants of the mechanistic proposal exist; however, the exact mechanism is still debated. Thus, using an ONIOM quantum mechanical/molecular mechanical approach, the mechanism by which uroporphyrinogen decarboxylase decarboxylates ring **D** of uroporphyrinogen-III has been investigated.

Structural and docking studies of *Leucaena leucocephala* Cinnamoyl CoA reductase

Nirmal K. Prasad [Goa University], Vaibhav Vindal, Vikash Kumar, Ashish Kabra and Navneet Phogat, et al.

J. Mol.Mod., **17**, 533–541, 2011.

Lignin, a major constituent of plant cell wall, is a phenolic heteropolymer. It plays a major role in the development of plants and their defense mechanism against pathogens. Cinnamoyl CoA reductase provides the substrates which represent the main transitional molecules of lignin biosynthesis pathway, exhibits a high in vitro kinetic preference for feruloyl CoA. In present study, the three-dimensional model of cinnamoyl CoA reductase was constructed based on the crystal structure of Grape Dihydroflavonol 4-Reductase.

Catalytic Roles of Active-Site Residues in 2-Methyl-3-hydroxypyridine-5-carboxylic Acid Oxygenase: An ONIOM/DFT Study

Boxue Tian, Åke Strid, and Leif A. Eriksson [National University of Ireland—Galway]

J. Phys. Chem. B., **115**, 1918–1926, 2011.

The catalytic mechanism of 2-methyl-3-hydroxypyridine-5-carboxylic acid (MHPC) oxygenase (MHPCO) has been systematically studied using DFT and ONIOM(DFT:MM) methods. MHPCO catalyzes the hydroxylation and subsequent ring-opening of the aromatic substrate MHPC to give the aliphatic product α -(N-acetylaminomethylene)succinic acid (AAMS). Our calculations show that the active-site residues Arg211 and Tyr223 have a minor effect on the reaction, while the peptide bond of Pro295–Ala296, the side chain of Tyr82 and several crystal water molecules affect the reaction energy profile considerably.

Protein-Protein Interactions

Using correlated parameters for improved ranking of protein-protein docking decoys

Pralay Mitra and Debnath Pal [Indian Institute of Science, Bangalore]

J. Comp. Chem. **32**, 787–796, 2011.

A successful protein-protein docking study culminates in identification of decoys at top ranks with near-native quaternary structures. In this work, we describe a novel method combining an interface-size filter, a regression model for geometric compatibility (based on two correlated surface and packing parameters), and normalized interaction energy (calculated from correlated nonbonded and solvation energies), to effectively rank decoys from a set of 10,000 decoys.

Scoring by Intermolecular Pairwise Propensities of Exposed Residues (SIPPER): A New Efficient Potential for Protein-Protein Docking

Carles Pons, David Talavera, Xavier de la Cruz, Modesto Orozco, and Juan Fernandez-Recio [Barcelona Supercomputing Center]

J.Chem. Infor. and Mod. **51**, 370–377, 2011.

A detailed and complete structural knowledge of the interactome is one of the grand challenges in Biology, and a variety of computational docking approaches have been developed to complement experimental efforts and help in the characterization of protein-protein interactions. In this study, we have extracted new statistical potentials from intermolecular pairs of exposed residues in known complex structures, which were then used to score protein-protein docking poses.

Membrane Proteins and Lipid Peptide Interactions

25-Hydroxycholesterol Increases the Availability of Cholesterol in Phospholipid Membranes

Brett N. Olsen, Paul H. Schlesinger, Daniel S. Ory, Nathan A. Baker [Pacific Northwest National Laboratory]

Biophysical Journal. **100**, 948-956, 2011.

Side-chain oxysterols are enzymatically generated oxidation products of cholesterol that serve a central role in mediating cholesterol homeostasis. Here we extend our previous work by using molecular-dynamics simulations of 25-HC and cholesterol mixtures in 1-palmitoyl-2-oleoyl-phosphatidylcholine bilayers to examine the combined effects of 25-HC and cholesterol in the same bilayer.

FCS Diffusion Laws in Two-Phase Lipid Membranes: Determination of Domain Mean Size by Experiments and Monte Carlo Simulations

Cyril Favard [Aix-Marseille Université], Jérôme Wenger, Pierre-François Lenne, Hervé Rigneault

Biophysical Journal. **100**, 1242-1251, 2011.

Many efforts have been undertaken over the last few decades to characterize the diffusion process in model and cellular lipid membranes. One of the techniques developed for this purpose, fluorescence correlation spectroscopy (FCS), has proved to be a very efficient approach, especially if the analysis is extended to measurements on different spatial scales (referred to as FCS diffusion laws). In this work, we examine the relevance of FCS diffusion laws for probing the behavior of a pure lipid and a lipid mixture at temperatures below, within and above the phase transitions, both experimentally and numerically.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Lateral Dynamics of Proteins with Polybasic Domain on Anionic Membranes: A Dynamic Monte-Carlo Study

Vladimir Yu. Kiselev, Davide Marenduzzo, Andrew B. Goryachev [University of Edinburgh]

Biophysical Journal. **100**, 1261-1270, 2011.

Positively charged polybasic domains are essential for recruiting multiple signaling proteins, such as Ras GTPases and Src kinase, to the negatively charged cellular membranes. Much less, however, is known about the influence of electrostatic interactions on the lateral dynamics of these proteins. We developed a dynamic Monte-Carlo automaton that faithfully simulates lateral diffusion of the adsorbed positively charged oligopeptides as well as the dynamics of mono-(phosphatidylserine) and polyvalent (PIP₂) anionic lipids within the bilayer.

A fast empirical GAFF compatible partial atomic charge assignment scheme for modeling interactions of small molecules with biomolecular targets

Goutam Mukherjee, Niladri Patra, Poranjyoti Barua and B. Jayaram [Indian Institute of Technology, Hauz Khas]

J. Comp. Chem. **32**, 893–907, 2011.

We report here a new and fast approach [Transferable Partial Atomic Charge Model (TPACM4)—upto four bonds] for deriving the partial atomic charges of small molecules for use in protein/DNA-ligand docking and scoring. We have created a look-up table of 5302 atom types to cover the chemical space of C, H, O, N, S, P, F, Cl, and Br atoms in small molecules together with their quantum mechanical RESP fit charges. The atom types defined span diverse plausible chemical environments of each atom in a molecule. The partial charge on any atom in a given molecule is then assigned by a reference to the look-up table.

Vesicle deformations by clusters of transmembrane proteins

Amir Houshang Bahrami [Sharif University of Technology] and Mir Abbas Jalali

Jou. Chem. Phys., **134**, 085106, 2011.

We carry out a coarse-grained molecular dynamics simulation of phospholipid vesicles with transmembrane proteins. We measure the mean and Gaussian curvatures of our protein-embedded vesicles and quantitatively show how protein clusters change the shapes of their host vesicles. The effects of depletion force and vesiculation on protein clustering are also investigated. Big clusters and highly aspherical vesicles cannot be formed when the fraction of protein to lipid molecules is large.

Inverted micelle formation of cell-penetrating peptide studied by coarse-grained simulation: Importance of attractive force between cell-penetrating peptides and lipid head group

Shuhei Kawamoto [Kanazawa University], Masako Takasu, Takeshi Miyakawa, Ryota Morikawa, Tatsuki Oda, Shiroh Futaki, and Hidemi Nagao

Jou. Chem. Phys., **134**, 095103, 2011.

Arginine-rich peptide and Antennapedia are cell-penetrating peptides (CPPs) which have the ability to permeate plasma membrane. Deformation of the plasma membrane with CPPs is the key to understand permeation mechanism. We investigate the dynamics of CPP and the lipid bilayer membrane by coarse-grained simulation. We found that the peptide makes inverted micelle in the lipid bilayer membrane, when the attractive potential between the peptide and lipid heads is strong. The translocation of the peptide suggests inverted micelle model as a possible mechanism of CPPs.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Theory and simulation on the kinetics of protein–ligand binding coupled to conformational change

Lu Cai [University of Science and Technology of China] and Huan-Xiang Zhou

Jou. Chem. Phys., **134**, 105101, 2011.

Conformational change during protein–ligand binding may significantly affect both the binding mechanism and the rate constant. Most earlier theories and simulations treated conformational change as stochastic gating with transition rates between reactive and nonreactive conformations uncoupled to ligand binding. Here we introduce a general model in which the energy surface of the protein in conformational space is coupled to ligand binding, and present a method for calculating the binding rate constant from Brownian dynamics simulations.

The Influence of Cholesterol on the Properties and Permeability of Hypericin Derivatives in Lipid Membranes

Emma S. E. Eriksson and Leif A. Eriksson [National University of Ireland—Galway]

J. Chem. Theor. and Comp., **7**, 560–574, 2011.

The promising photosensitizing properties of hypericin, a natural quinine substituted with hydroxyl and alkyl groups, have led to the proposal that it can be utilized in photodynamic therapy. The behavior of hypericin derivatives in a pure dipalmitoylphosphatidylcholine (DPPC) lipid membrane has recently been studied theoretically by means of molecular dynamics simulations. In the present study, we investigated hypericin and its brominated derivatives in membranes containing 9 and 25 mol % cholesterol.

Formal Estimation of Errors in Computed Absolute Interaction Energies of Protein–Ligand Complexes

John C. Faver, Mark L. Benson, Xiao He, Benjamin P. Roberts, Bing Wang, Michael S. Marshall, Matthew R. Kennedy, C. David Sherrill, and Kenneth M. Merz, Jr. [The University of Florida]

J. Chem. Theor. and Comp., **7**, 790–797, 2011.

A largely unsolved problem in computational biochemistry is the accurate prediction of binding affinities of small ligands to protein receptors. We present a detailed analysis of the systematic and random errors present in computational methods through the use of error probability density functions, specifically for computed interaction energies between chemical fragments comprising a protein–ligand complex. An HIV–II protease crystal structure with a bound ligand (indinavir) was chosen as a model protein–ligand complex.

Influence of Chloroform in Liquid-Ordered and Liquid-Disordered Phases in Lipid Membranes

Ramon Reigada [Universitat de Barcelona]

J. Phys. Chem. B., **115**, 2527–2535, 2011.

Molecular dynamics simulations are used to study the influence of chloroform in two different lipid membranes: one representative of a liquid-disordered phase and another one mixed with cholesterol and representative of a liquid-ordered phase. When chloroform is added to the cholesterol-containing membrane, a strong chain disordering is induced. In both cases, chloroform laterally disorganizes the membranes. The analysis of the main structural and dynamical membrane properties reveals that the interaction with cholesterol is the main factor to explain the strong disordering effect of chloroform in liquid-ordered phases.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Effect of flanking residues on the conformational sampling of the internal fusion peptide from Ebola virus

Adam J. Jaskierny, Afra Panahi and Michael Feig [Michigan State University]

Proteins: Stru. Fun. and Bioinfo. **79**, 1109–1117, 2011.

Fusion peptides mediate viral and host-cell membrane fusion during viral entry. The monomeric form of the internal fusion peptide from Ebola virus was studied in membrane bilayer and water environments with computer simulations using replica exchange sampling and an implicit solvent description of the environment. Wild-type Ebola fusion peptide (EFP), the W8A mutant form, and an extended construct with flanking residues were examined.

Nucleic Acids

Internucleotide J-couplings and chemical shifts of the N—H···N hydrogen-bonds in the radiation-damaged guanine-cytosine base pairs

Huifang Li, Laibin Zhang, Li Han, Wenming Sun and Yuxiang Bu [Shandong University]

J. Comp. Chem. **32**, 1159–1169, 2011.

Internucleotide $^2hJ_{NN}$ spin-spin couplings and chemical shifts ($\delta(^1H)$ and $\Delta\delta(^{15}N)$) of N—H···N H-bond units in the natural and radiation-damaged G-C base pairs were predicted using the appropriate density functional theory calculations with a large basis set. Four possible series of the damaged G-C pairs (viz., dehydrogenated and deprotonated G-C pairs, $GC^{\cdot-}$ and $GC^{\cdot+}$ radicals) were discussed carefully in this work. This study provides a correlation of the properties of the damaged DNA species with some of the electronic parameters associated with the NMR spectra for the understanding of the different state character of the damaged DNA bases.

Numerical study of DNA-functionalized microparticles and nanoparticles: Explicit pair potentials and their implications for phase behavior

Mirjam E. Leunissen [FOM Institute AMOLF] and Daan Frenkel

Jou. Chem. Phys., **134**, 084702, 2011.

DNA-coated colloids have great potential for the design of complex self-assembling materials. In order to predict the structures that will form, knowledge of the interactions between DNA-functionalized particles is crucial. We report results from Monte Carlo simulations of the pair-interaction between particles coated with single-stranded DNA sticky ends that are connected to the surface by relatively short and stiff surface tethers. We complement our calculations with a study of the interaction between two planar surfaces coated with the same DNA.

Effect of Surface Binding on Heterogeneous DNA Melting Equilibria: A Monte Carlo Simulation Study

John H. Allen, Emily T. Schoch, and John M. Stubbs [The University of New England]

J. Phys. Chem. B., **115**, 1720–1726, 2011.

DNA microarrays are constructed with a surface-immobilized single-stranded probe sequence that hydrogen bonds with its complementary target strand from solution and is subsequently detected, making their hybridization equilibrium of central importance. Unexpectedly, the effect of surface immobilization is that if the sequences of probe and target are exchanged, the hybridization equilibrium shifts. Here, configurational-bias Monte Carlo simulations using a coarse-grained model for DNA were carried out for an undecamer double helix both in solution and bound to a surface to determine dissociation equilibria.

Nucleic Acids (Cont'd)

Molecular Dynamics Study and Electronic Structure Evolution of a DNA Duplex d(CCCGATCGGG)₂

Basab Chattopadhyay and Monika Mukherjee [Indian Association for the Cultivation of Science]

J. Phys. Chem. B., **115**, 1760–1766, 2011.

The molecular dynamics simulations and electronic structure evolution of a A-DNA decamer, d(CCCGATCGGG)₂, in the presence and absence of [Co(NH₃)₆]³⁺ ions have been investigated. In both cases, the results of 2.5 ns MD simulation indicate a A-DNA → B-DNA transition. Ab initio DFT calculations were performed on a series of conformations representing the A → B transitions to reveal the dynamical behavior of the electronic structure of the decamer.

DNA Melting in Slit Pores: A Reaction Density Functional Theory

Yu Liu, Yazhuo Shang, Honglai Liu [East China University of Science and Technology], Ying Hu, and Jianwen Jiang

J. Phys. Chem. B., **115**, 1720–1726, 2011.

A reaction density functional theory (R-DFT) is developed for chemical reactions in confined space by integrating reaction thermodynamics and DFT for chain fluids. The theory is applied to investigate DNA melting in slit pores, with nucleotides represented by coarse-grained charged Lennard-Jones particles. Three types of slit pores are considered for DNA melting: repulsive pore, attractive pore, and under electric field. In repulsive pores, the melting temperature increases slightly with reducing pore width, and the increase magnitude is nearly the same for DNA of different chain lengths.

Single Strand Break in DNA Coupled to the O—P Bond Cleavage. A Computational Study

Janusz Rak, Monika Kobylecka, and Piotr Storoniak [University of Gdansk]

J. Phys. Chem. B., **115**, 1911–1917, 2011.

In the present study, we consider the formation of a single strand break (SSB) in DNA via an alternative mechanism involving O—P bond splitting that was observed as a minor route to DNA damage induced by low-energy electrons (LEEs) or γ radiation. We postulate and characterize, at the B3LYP/6-31++G** level, a path that starts with LEE attachment to the nucleotide of thymine resulting in a stable valence radical anion localized on pyrimidine. In the next step, a proton is attached to the C5 position of thymine, producing a neutral monohydroradical of this nucleotide.

Surfaces, Catalysts, and Materials Subjects

Molecular Dynamics Simulations of SDS, DTAB, and C₁₂E₈ Monolayers Adsorbed at the Air/Water Surface in the Presence of DSEP

Jinyu Pang, Yajing Wang, Guiying Xu [Shandong University], and Tingting Han, Xin Lv and Jian Zhang

J. Phys. Chem. B., **115**, 2518–2526, 2011.

The properties of adsorbed monolayers of three hydrocarbon surfactants with the same hydrophobic tail, sodium dodecyl sulfate (SDS), dodecyltrimethylammonium bromide (DTAB) and octaethylene glycol dodecyl ether (C₁₂E₈) at the air/water surface in the absence and presence of a dimethylsiloxane ethoxylate-propoxylate (DSEP) were studied via molecular dynamics simulations to compare the effect of the headgroups on the aggregation behaviors of surfactant mixtures.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Design of semisynthetic analogues and 3D-QSAR study of eunicellin-based diterpenoids as prostate cancer migration and invasion inhibitors

Hossam M. Hassan, Ahmed Y. Elnagar, Mohammad A. Khanfar, Asmaa A. Sallam, Rabab Mohammed, Lamiaa A. Shaala, Diaa T.A. Youssef, Mohamed S. Hifnawy, Khalid A. El Sayed [University of Louisiana at Monroe]

Europ. Biophys. Jou., **46**, 1122-1130, 2011.

Prostrate cancer constitutes the second leading cause of cancer deaths in men in United States. Eunicellin-based diterpenoids are important bioactive marine natural products isolated from corals of alcyonaria species. CoMFA and CoMSIA were performed using SYBYL 8.1 program package to create a valid 3D-QSAR model to guide future design of potent eunicellin diterpenes cancer migration inhibitors. Eunicellin-based diterpenes are potential marine natural hits appropriate for optimization as inhibitors of metastatic prostate cancer.

Development of Novel 3D-QSAR Combination Approach for Screening and Optimizing B-Raf Inhibitors in silico

Kuei-Chung Shih, Chun-Yuan Lin [Chang Gung University], Jiayi Zhou, Hsiao-Chieh Chi, Ting-Shou Chen, Chun-Chung Wang, Hsiang-Wen Tseng, and Chuan-Yi Tang

J.Chem. Infor. and Mod. **51**, 398–407, 2011.

B-Raf is a member of the RAF family of serine/threonine kinases: it mediates cell division, differentiation, and apoptosis signals through the RAS-RAF-MAPK pathway. Thus, B-Raf is of keen interest in cancer therapy, such as melanoma. In this study, we propose the first combination approach to integrate the pharmacophore (PhModel), CoMFA, and CoMSIA models for B-Raf, and this approach could be used for screening and optimizing potential B-Raf inhibitors in silico. Ten PhModels were generated based on the HypoGen BEST algorithm with the flexible fit method and diverse inhibitor structures.

Quantitative structure–activity relationship analysis of β -amyloid aggregation inhibitors

Shiri Stempler [Tel Aviv University], Michal Levy-Sakin, Anat Frydman-Marom, Yaniv Amir and Roni Scherzer-Attali, et al.

J. Comp. Aided Mol. Des. **25**, 135-144, 2011.

Inhibiting the aggregation process of the β -amyloid peptide is a promising strategy in treating Alzheimer's disease. In this work, we have collected a dataset of 80 small molecules with known inhibition levels and utilized them to develop two comprehensive quantitative structure–activity relationship models: a Bayesian model and a decision tree model. These models have exhibited high predictive accuracy: 87% of the training and test sets using the Bayesian model and 89 and 93% of the training and test sets, respectively, by the decision tree model.

Rethinking 3D-QSAR

Richard D. Cramer [Tripos, Inc.]

J. Comp. Aided Mol. Des. **25**, 197-201, 2011.

The average error of pIC50 prediction reported for 140 structures in make-and-test applications of topomer CoMFA by four discovery organizations is 0.5. This remarkable accuracy can be understood to result from a topomer pose's goal of generating field differences only at lattice intersections adjacent to intended structural change.

Potentials and Parameters

A reoptimized GROMOS force field for hexopyranose-based carbohydrates accounting for the relative free energies of ring conformers, anomers, epimers, hydroxymethyl rotamers, and glycosidic linkage conformers

Halvor S. Hansen and Philippe H. Hünenberger
[Laboratorium für Physikalische Chemie, ETH Zürich]

J. Comp. Chem. **32**, 998–1032, 2011.

This article presents a reoptimization of the GROMOS 53A6 force field for hexopyranose-based carbohydrates (nearly equivalent to 45A4 for pure carbohydrate systems) into a new version 56A_{CARBO} (nearly equivalent to 53A6 for non-carbohydrate systems). This reoptimization was found necessary to repair a number of shortcomings of the 53A6 (45A4) parameter set and to extend the scope of the force field to properties that had not been included previously into the parameterization procedure.

Molecular Dynamics

Photosynthetic Light-Harvesting Is Tuned by the Heterogeneous Polarizable Environment of the Protein

Carles Curutchet [Universitat de Girona], Jacob Kongsted, Aurora Muñoz-Losa, Hoda Hossein-Nejad, Gregory D. Scholes, and Benedetta Mennucci

J. Am. Chem. Soc., **133**, 3078–3084, 2011.

In photosynthesis, special antenna proteins that contain multiple light-absorbing molecules (chromophores) are able to capture sunlight and transfer the excitation energy to reaction centers with almost 100% quantum efficiencies. Here, we present a combined quantum chemical/molecular mechanical approach to compute electronic couplings that accounts for the heterogeneous dielectric nature of the protein–solvent environment in atomic detail. We apply the method to study the effect of dielectric heterogeneity in the energy migration properties of the PE545 principal light-harvesting antenna of the cryptomonad *Rhodomonas* CS24.

The opsin shift and mechanism of spectral tuning in rhodopsin

Ramkumar Rajamani, Yen-Lin Lin and Jiali Gao [University of Minnesota]

J. Comp. Chem. **32**, 854–865, 2011.

Molecular dynamics simulations and combined quantum mechanical and molecular mechanical calculations have been performed to investigate the mechanism of the opsin shift and spectral tuning in rhodopsin. A red shift of -980 cm^{-1} was estimated in the transfer of the chromophore from methanol solution environment to the protonated Schiff base (PSB)-binding site of the opsin. The conformational change from a 6-s-cis-all-trans configuration in solution to the 6-s-cis-11-cis conformer contributes additional -200 cm^{-1} , and the remaining effects were attributed to dispersion interactions with the aromatic residues in the binding site.

A simple, efficient polarizable coarse-grained water model for molecular dynamics simulations

Sereina Riniker [Swiss Federal Institute of Technology] and Wilfred F. van Gunsteren

Jou. Chem. Phys., **134**, 084110, 2011.

The development of coarse-grained (CG) models that correctly represent the important features of compounds is essential to overcome the limitations in time scale and system size currently encountered in atomistic molecular dynamics simulations. Experimental and all-atom simulated data of liquid water at room temperature are used for parametrization of the model. The experimental density and the relative static dielectric permittivity were chosen as primary target properties.

Molecular Dynamics (Cont'd)

A Coarse-Grained Model for Molecular Dynamics Simulations of Native Cellulose

Jakob Wohler [Royal Institute of Technology, SE-10044 Stockholm] and Lars A. Berglund

J. Chem. Theor. and Comp., **7**, 753–760, 2011.

We have constructed a coarse-grained model of crystalline cellulose to be used in molecular dynamics simulations. Using cellobiose from the recently published MARTINI coarse-grained force field for carbohydrates [Lopez, C. A. et al. *J. Chem. Theory Comput.* 2009, **5**, 3195–3210] as a starting point, we have reparameterized the nonbonded interactions to reproduce the partitioning free energies between water and cyclohexane for a series of celooligomers, cellobiose through cellopentaose.

On-the-Fly Identification of Conformational Substates from Molecular Dynamics Simulations

Arvind Ramanathan, Ji Oh Yoo, and Christopher J. Langmead [Carnegie Mellon University]

J. Chem. Theor. and Comp., **7**, 778–789, 2011.

We recently introduced a new method for discovering, characterizing, and monitoring spatiotemporal patterns in the conformational fluctuations in molecular dynamics simulation data (*J. Comput. Biol.* 2010, **17** (3), 309–324). Significantly, our method, called Dynamic Tensor Analysis (DTA), can be performed as the simulation is progressing. In this paper, we demonstrate that the patterns discovered by DTA often correspond to functionally important conformational substates.

Monte Carlo

Exploiting Configurational Freezing in Nonequilibrium Monte Carlo Simulations

Paolo Nicolini, Diego Frezzato, and Riccardo Chelli [Universita di Firenze]

J. Chem. Theor. and Comp., **7**, 582–593, 2011.

To achieve acceptable accuracy in fast-switching free energy estimates by Jarzynski equality [*Phys. Rev. Lett.* 1997, **78**, 2690] or Crooks fluctuation theorem [*J. Stat. Phys.* 1998, **90**, 1481], it is often necessary to realize a large number of externally driven trajectories. We propose a computational technique, addressed to Monte Carlo simulations, to improve free energy estimates by lowering the dissipated work. The method is inspired by the dynamical freezing approach, recently developed in the context of molecular dynamics simulations.

Free Energy Perturbation

A free-energy perturbation method based on Monte Carlo simulations using quantum mechanical calculations (QM/MC/FEP method): Application to highly solvent-dependent reactions

Kenji Hori [Yamaguchi University], Toru Yamaguchi, Keita Uezu and Michinori Sumimoto

J. Comp. Chem. **32**, 778–786, 2011.

This study describes the framework of the quantum mechanical (QM)/Monte Carlo (MC)/free-energy perturbation (FEP) method, a FEP method based on MC simulations using quantum chemical calculations. Because a series of structures generated by interpolating internal coordinates between transition state and reactant did not produce smooth free-energy profiles, we used structures from the intrinsic reaction coordinate calculations. This method was first applied to the Diels–Alder reaction between methyl vinyl ketone and cyclopentadiene and produced $\Delta G_{\text{sol}}^{\ddagger}$ values of 20.1 and 21.4 kcal mol^{−1} in aqueous and methanol solutions, respectively.

Free Energy Perturbation (Cont'd)

Combining non-Boltzmann sampling with free energy perturbation to calculate free energies of hydration of quantum models from a simulation of an approximate model

Robert H. Wood [University of Delaware] and Haitao Dong

Jou. Chem. Phys., **134**, 101101, 2011.

This paper proposes combining non-Boltzmann sampling with free energy perturbation to allow calculations of the free energy of hydration of a solute with both solute–water and water–water interactions with the nearest waters calculated by high-level quantum models. The method involves simulation of an approximate model of all interactions and uses both free energy perturbation and non-Boltzmann sampling to calculate the difference in energy between the approximate and quantum models.

Free-energy landscape of the GB1 hairpin in all-atom explicit solvent simulations with different force fields: Similarities and differences

Robert B. Best [Lehigh University] and Jeetain Mittal

Proteins: Stru. Fun. and Bioinfo. **79**, 1318–1328, 2011.

Although it is now possible to fold peptides and miniproteins in molecular dynamics simulations, it is well appreciated that force fields are not all transferable to different proteins. Here, we investigate the influence of the protein force field and the solvent model on the folding energy landscape of a prototypical two-state folder, the GB1 hairpin. We use extensive replica-exchange molecular dynamics simulations to characterize the free-energy surface as a function of temperature.

QM and QM/MM

Structure and dynamics of methanol in water: A quantum mechanical charge field molecular dynamics study

Syed Tarique Moin, Thomas S. Hofer, Bernhard R. Randolph and Bernd M. Rode [University of Innsbruck]

J. Comp. Chem. **32**, 886–892, 2011.

An ab initio quantum mechanical charge field molecular dynamics simulation was carried out for one methanol molecule in water to analyze the structure and dynamics of hydrophobic and hydrophilic groups. It is found that water molecules around the methyl group form a cage-like structure whereas the hydroxyl group acts as both hydrogen bond donor and acceptor, thus forming several hydrogen bonds with water molecules. The dynamic analyses correlate well with the structural data, evaluated by means of radial distribution functions, angular distribution functions, and coordination number distributions.

A minimal implementation of the AMBER–GAUSSIAN interface for ab initio QM/MM-MD simulation

Takuya Okamoto, Kenta Yamada, Yoshiyuki Koyano, Toshio Asada, Nobuaki Koga and Masataka Nagaoka [Nagoya University]

J. Comp. Chem. **32**, 771–777, 2011.

For applying to a number of theoretical methodologies based on an ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics method connecting AMBER9 with GAUSSIAN03, we have developed an AMBER–GAUSSIAN interface (AG-IF), which can be one of the simplest architectures. In the AG-IF, only a few subroutines addition is necessary to retrieve the QM/MM energy and forces, obtained by GAUSSIAN, for solving a set of Newtonian equations of motion in AMBER.

QM and QM/MM (Cont'd)

Antitumor activity of bent metallocenes: electronic structure analysis using DFT computations

Dhurairajan Senthilnathan, Sundararajan Vaideeswaran, Ponnambalam Venuvanalingam [Bharathidasan University] and Gernot Frenking

J. Mol.Mod., **17**, 465-475, 2011.

The antitumor activities of bent metallocenes $[\text{Cp-M-Cp}]^{2+}$ ($\text{M} = \text{Ti}, \text{V}, \text{Nb}, \text{Mo}$) and complexes of them with guanine, adenine, thymine and cytosine nucleotides have been probed using electronic structure calculations. DFT/BP86 calculations have revealed that the bent metallocene-nucleotide interaction strongly depends on the stability of the hydrolyzed form of the bent metallocene dichloride $[\text{Cp}_2\text{M}]^{2+}$ species, and in turn the stability of the $[\text{Cp}_2\text{M}]^{2+}$ species strongly depends on the electronic structure of $[\text{Cp}_2\text{M}]^{2+}$.

Transferable scoring function based on semiempirical quantum mechanical PM6-DH2 method: CDK2 with 15 structurally diverse inhibitors

Petr Dobeš, Jindřich Fanfrlík, Jan Řezáč, Michal Otyepka and Pavel Hobza [Palacký University]

J. Comp. Aided Mol. Des. **25**, 223-235, 2011.

A semiempirical quantum mechanical PM6-DH2 method accurately covering the dispersion interaction and H-bonding was used to score fifteen structurally diverse CDK2 inhibitors. The geometries of all the complexes were taken from the X-ray structures and were reoptimised by the PM6-DH2 method in continuum water. The total scoring function was constructed as an estimate of the binding free energy, i.e., as a sum of the interaction enthalpy, interaction entropy and the corrections for the inhibitor desolvation and deformation energies.

Clarification of the Mechanism of Acylation Reaction and Origin of Substrate Specificity of the Serine-Carboxyl Peptidase Sedolisin through QM/MM Free Energy Simulations

Qin Xu, Jianzhuang Yao, Alexander Wlodawer, and Hong Guo [University of Tennessee, Knoxville]

J. Phys. Chem. B., **115**, 2470–2476, 2011.

Quantum mechanical/molecular mechanical (QM/MM) free energy simulations are applied for understanding the mechanism of the acylation reaction catalyzed by sedolisin, a representative serine-carboxyl peptidase, leading to the acyl-enzyme (AE) and first product from the enzyme-catalyzed reaction. One of the interesting questions to be addressed in this work is the origin of the substrate specificity of sedolisin that shows a relatively high activity on the substrates with Glu at P_1 site. It is shown that the bond making and breaking events of the acylation reaction involving a peptide substrate (LLE*FL) seem to be accompanied by local conformational changes, proton transfers as well as the formation of alternative hydrogen bonds.

Ligand Docking

On the Origin of the Stronger Binding of PIB over Thioflavin T to Protofibrils of the Alzheimer Amyloid- β Peptide: A Molecular Dynamics Study

Chun Wu, Michael T. Bowers, Joan-Emma Shea [University of California]

Biophysical Journal. **100**, 1316-1324, 2011.

Pittsburgh compound B (PIB) is a neutral derivative of the fluorescent dye Thioflavin T (ThT), which displays enhanced hydrophobicity and binding affinity to amyloid fibrils. We present molecular dynamics simulations of binding of PIB and ThT to a common cross- β -subunit of the Alzheimer Amyloid- β peptide ($A\beta$). Our simulations of binding to $A\beta_{9-40}$ protofibrils show that PIB, like ThT, selectively binds to the hydrophobic or aromatic surface grooves on the β -sheet surface along the fibril axis.

Assessing the performance of the molecular mechanics/Poisson Boltzmann surface area and molecular mechanics/generalized Born surface area methods. II. The accuracy of ranking poses generated from docking

Tingjun Hou [Soochow University], Junmei Wang, Youyong Li and Wei Wang

J. Comp. Chem. **32**, 866–877, 2011.

In molecular docking, it is challenging to develop a scoring function that is accurate to conduct high-throughput screenings. Most scoring functions implemented in popular docking software packages were developed with many approximations for computational efficiency, which sacrifices the accuracy of prediction. With advanced technology and powerful computational hardware nowadays, it is feasible to use rigorous scoring functions, such as molecular mechanics/Poisson Boltzmann surface area (MM/PBSA) and molecular mechanics/generalized Born surface area (MM/GBSA) in molecular docking studies. Here, we systematically investigated the performance of MM/PBSA and MM/GBSA to identify the correct binding conformations and predict the binding free energies for 98 protein–ligand complexes.

A Unified, Probabilistic Framework for Structure- and Ligand-Based Virtual Screening

Steven L. Swann, Scott P. Brown, Steven W. Muchmore, Hetal Patel, Philip Merta, John Locklear, and Philip J. Hajduk [Abbott Laboratories]

J. Med. Chem. **54**, 1223–1232, 2011.

We present a probabilistic framework for interpreting structure-based virtual screening that returns a quantitative likelihood of observing bioactivity and can be quantitatively combined with ligand-based screening methods to yield a cumulative prediction that consistently outperforms any single screening metric. The approach has been developed and validated on more than 30 different protein targets.

Ab initio studies on the decomposition kinetics of CF₃OCF₂O radical

Hari Ji Singh [DDU Gorakhpur University] and Bhupesh Kumar Mishra

J. Mol. Mod., **17**, 415-422, 2011.

To probe the selective mechanism of agonists binding to three opioid receptor subtypes, ligand-based and receptor-based methods were implemented together and subtype characteristics of opioid agonists were clearly described. Three pharmacophore models of opioid agonists were generated by the Catalyst/HypoGen program. The best pharmacophore models for μ , δ and κ agonists contained four, five and five features, respectively.

Ligand Docking (Cont'd)

StructRank: A New Approach for Ligand-Based Virtual Screening

Fabian Rathke [University of Technology, Berlin], Katja Hansen, Ulf Brefeld, and Klaus-Robert Muller

J.Chem. Infor. and Mod. **51**, 83–92, 2011.

Screening large libraries of chemical compounds against a biological target, typically a receptor or an enzyme, is a crucial step in the process of drug discovery. Virtual screening (VS) can be seen as a ranking problem which prefers as many actives as possible at the top of the ranking. As a standard, current QSAR models apply regression methods to predict the level of activity for each molecule and then sort them to establish the ranking. In this paper, we propose a top-k ranking algorithm (StructRank) based on Support Vector Machines to solve the early recognition problem directly.

Quantum Mechanics/Molecular Mechanics Strategies for Docking Pose Refinement: Distinguishing between Binders and Decoys in Cytochrome c Peroxidase

Steven K. Burger [McMaster University], David C. Thompson, and Paul W. Ayers

J.Chem. Infor. and Mod. **51**, 93–101, 2011.

We investigate the effect of systematically applying molecular dynamics (MD) and quantum mechanics/molecular mechanics (QM/MM) to docked poses in an attempt to improve the correspondence between theoretical prediction and experimental observation. The proposed scheme involves running a short time scale MD simulation on a docked ligand pose (and any known structurally important crystal structure waters in the active site), followed by QM/MM minimization.

The molecular mechanism studies of chirality effect of PHA-739358 on Aurora kinase A by molecular dynamics simulation and free energy calculations

Yuanhua Cheng, Wei Cui, Quan Chen, Chen-Ho Tung and Mingjuan Ji and Fushi Zhang [Tsinghua University]

J. Comp. Aided Mol. Des. **25**, 171-180, 2011.

Aurora kinase family is one of the emerging targets in oncology drug discovery and several small molecules targeting aurora kinases have been discovered and evaluated under early phase I/II trials. In present study, the mechanism of how different configurations influence the binding affinity was investigated using molecular dynamics (MD) simulations, free energy calculations and free energy decomposition analysis. The predicted binding free energies of these two complexes are consistent with the experimental data.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 32(5), April, 2011.

- 771–777 **A theoretical survey on the structures, energetics, and isomerization pathways of the B₅O radical**, Chang-Bin Shao, Lin Jin and Yi-Hong Ding [Jilin University]

Boron-centered radicals have received growing interest. Recently, two groups reported density functional theory investigations (GGA-PW91 and B3LYP) on a hexa-atomic boron-oxide radical, B₅O, which has led to great discrepancies on the type of low-lying structures. In this article, we not only explore the energetics of doublet and quartet B₅O isomers at high electron-correlated levels (CCSD(T)/6-311+G(2df), CCSD(T)/aug-cc-pVTZ, and G3B3) but also investigate the isomerization and fragmentation stability of the low-lying B₅O isomers.

- 778–786 **A free-energy perturbation method based on Monte Carlo simulations using quantum mechanical calculations (QM/MC/FEP method): Application to highly solvent-dependent reactions**, Kenji Hori [Yamaguchi University], Toru Yamaguchi, Keita Uezu and Michinori Sumimoto

See Methodology / Free energy perturbations.

- 787–796 **Using correlated parameters for improved ranking of protein–protein docking decoys**, Pralay Mitra and Debnath Pal [Indian Institute of Science, Bangalore]

See Applications / Protein Protein Interactions.

- 797–809 **Intermolecular potential energy surface for CS₂ dimer**, Hossein Farrokhpour [Isfahan University of Technology], Zainab Mombeini, Mansoor Namazian and Michelle L. Coote

A new four-dimensional intermolecular potential energy surface for CS₂ dimer is obtained by ab initio calculation of the interaction energies for a range of configurations and center-of-mass separation distances for the first time. The calculations were performed using the supermolecular approach at the Møller–Plesset second-order perturbation (MP2) level of theory with the augmented correlation consistent basis sets (aug-cc-pVxZ, x = D, T) and corrected for the basis-set superposition error using the full counterpoise correction method.

- 810–815 **Efficient quantification of the importance of contacts for the dynamical stability of proteins**, Kay Hamacher [TU Darmstadt]

See Applications / Protein Dynamics.

- 816–821 **Improving the Wang–Landau algorithm for polymers and proteins**, Adam D. Swetnam and Michael P. Allen [University of Warwick]

See Applications / Protein Dynamics.

- 822–834 **The first branching point in porphyrin biosynthesis: A systematic docking, molecular dynamics and quantum mechanical/molecular mechanical study of substrate binding and mechanism of uroporphyrinogen-III decarboxylase**, Eric A. C. Bushnell, Edwin Erdtman, Jorge Llano, Leif A. Eriksson and James W. Gauld [University of Windsor]

See Applications / Enzyme catalysis.

- 835–853 **A novel predictive model for formation enthalpies of Si and Ge hydrides with propane- and butane-like structures**, C. Weng, J. Kouvetakis and A. V. G. Chizmeshya [Arizona State University]

Butane- and propane-like silicon–germanium hydrides and chlorinated derivatives represent a new class of precursors for the fabrication of novel metastable materials at low-temperature regimes compatible with selective growth and commensurate with the emerging demand for the reduced thermal budgets of complementary metal oxide semiconductor integration. Accordingly, here we develop a method to accurately predict the formation enthalpy of these compounds using atom-wise corrections for Si, Ge, Cl, and H.

- 854–865 **The opsin shift and mechanism of spectral tuning in rhodopsin**, Ramkumar Rajamani, Yen-Lin Lin and Jiali Gao [University of Minnesota]

See Methodology / Molecular Dynamics.

- 866–877 **Assessing the performance of the molecular mechanics/Poisson Boltzmann surface area and molecular mechanics/generalized Born surface area methods. II. The accuracy of ranking poses generated from docking**, Tingjun Hou [Soochow University], Junmei Wang, Youyong Li and Wei Wang

See Methodology / Ligand Docking.

- 878–885 **Electrostatic solvation free energy of amino acid side chain analogs: Implications for the validity of electrostatic linear response in water**, Bin Lin and B. Montgomery Pettitt [Baylor College of Medicine]

See Applications / Free energy calculations.

- 886–892 **Structure and dynamics of methanol in water: A quantum mechanical charge field molecular dynamics study**, Syed Tarique Moin, Thomas S. Hofer, Bernhard R. Randolph and Bernd M. Rode [University of Innsbruck]

See Methodology / QM and QM/MM.

- 893–907 **A fast empirical GAFF compatible partial atomic charge assignment scheme for modeling interactions of small molecules with biomolecular targets**, Goutam Mukherjee, Niladri Patra, Poranjyoti Barua and B. Jayaram [Indian Institute of Technology, Hauz Khas]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 908–914 **Electronic and vibrational linear and nonlinear polarizabilities of Li@C₆₀ and [Li@C₆₀]⁺** H. Reis [The National Hellenic Research Foundation], O. Loboda, A. Avramopoulos, M. G. Papadopoulos, B. Kirtman, J. M. Luis and R. Zaleśny

Electronic and vibrational nuclear relaxation (NR) contributions to the dipole (hyper)polarizabilities of the endohedral fullerene Li@C₆₀ and its monovalent cation [Li@C₆₀]⁺ are calculated at the (U)B3LYP level.

- 915–931 **Computerized evaluation of mean residence times in multicompartmental linear system and pharmacokinetics**, J. M. Villalba, A. J. Barbero, R. Diaz-Sierra, E. Arribas, M. J. Garcia-Meseguer, F. Garcia-Sevilla, M. Garcia-Moreno, J. A. Vidal De Labra and R. Varon [Universidad de Castilla-La Mancha]

See Applications / Bioinformatics and Cheminformatics.

- 932–942 **A minimal implementation of the AMBER–GAUSSIAN interface for ab initio QM/MM-MD simulation**, Takuya Okamoto, Kenta Yamada, Yoshiyuki Koyano, Toshio Asada, Nobuaki Koga and Masataka Nagaoka [Nagoya University]

See Methodology / QM and QM/MM.

- 943–952 **Looking for high energy density compounds applicable for propellant among the derivatives of dpo with —n₃, —ono₂, and —nno₂ groups**, Gui-Xiang Wang [Nanjing University of Science and Technology], Xue-Dong Gong, Yan Liu, Hong-Chen Du, Xiao-Juan Xu and He-Ming Xiao

The derivatives of DPO (2,5-dipicryl-1,3,4-oxadiazole) are optimized to obtain their molecular geometries and electronic structures at the DFT-B3LYP/6-31G* level.

- 953–966 **Rapid evaluation of the binding energies in hydrogen-bonded amide–thymine and amide–uracil dimers in gas phase**, Yang Li, Xiao-Nan Jiang and Chang-Sheng Wang [Liaoning Normal University]

See Applications / Ligand Binding.

- 967–977 **Multipole electrostatics in hydration free energy calculations**, Yue Shi, Chuanjie Wu, Jay W. Ponder and Pengyu Ren [The University of Texas]

See Applications / Free energy calculations.

Journal of Computational Chemistry, 32(6), April, 2011.

- 987–997 **Theoretical study on the kinetics of OH radical reactions with CH₃OOH and CH₃CH₂OOH**, Jie Luo, Xiujuan Jia, Yang Gao, Guicai Song, Yanbo Yu, Rongshun Wang and Xiumei Pan [Northeast Normal University]

The mechanisms and kinetics studies of the OH radical with alkyl hydroperoxides CH₃OOH and CH₃CH₂OOH reactions have been carried out theoretically.

- 998–1032 **A reoptimized GROMOS force field for hexopyranose-based carbohydrates accounting for the relative free energies of ring conformers, anomers, epimers, hydroxymethyl rotamers, and glycosidic linkage conformers**, Halvor S. Hansen and Philippe H. Hünenberger [Laboratorium für Physikalische Chemie, ETH Zürich]

See Methodology / Potentials and Parameters.

- 1033–1042 **Theoretical study on phosphorescence efficiency and color tuning from orange to blue-green of Ir(III) complexes based on substituted 2-phenylimidazo[1,2-a]pyridine ligand**, Xiao-Na Li, Zhi-Jian Wu, Xi-Yan Li, Hong-Jie Zhang [Chinese Academy of Sciences] and Xiao-Juan Liu

The geometrical structures, phosphorescence quantum yields, and electroluminescence (EL) efficiency of six iridium(III) complexes containing 2-phenylimidazo[1,2-a]pyridine ligand are investigated by density functional theory (DFT), which show a wide color tuning of photoluminescence from orange ($\lambda_{\text{em}} = 550$ nm) to blue-green ($\lambda_{\text{em}} = 490$ nm).

- 1043–1053 **Crystal molecular dynamics simulations to speed up MM/PB(GB)SA evaluation of binding free energies of di-mannose deoxy analogs with P51G-m4-Cyanovirin-N**, Ivan I. Vorontsov and Osamu Miyashita [University of Arizona]

See Applications / Ligand Binding.

- 1054–1064 **Energy partitioning scheme based on self-consistent method for subsystems: Populational space approach**, Piotr De Silva and Jacek Korchowiec [Jagiellonian University]

The refinement of the previously proposed energy partitioning scheme, self-consistent charge and configuration method for subsystems (Korchowiec and Uchimaru, J Chem Phys 2000, 112, 1623), is proposed.

- 1065–1081 **Computational study on the reactions of H₂O₂ on TiO₂ anatase (101) and rutile (110) surfaces**, Wen-Fei Huang, P. Raghunath and M. C. Lin [National Chiao Tung University]

This study investigates the adsorption and reactions of H₂O₂ on TiO₂ anatase (101) and rutile (110) surfaces by first-principles calculations based on the density functional theory in conjunction with the projected augmented wave approach, using PW91, PBE, and revPBE functionals.

- 1082–1090 **Non-Boltzmann sampling and Bennett's acceptance ratio method: How to profit from bending the rules**, Gerhard König and Stefan Boresch [University of Vienna]

The exact computation of free energy differences requires adequate sampling of all relevant low energy conformations. We demonstrate that this can be accomplished quite simply with a slight modification of Bennett's Acceptance Ratio method, referring to this technique as Non-Boltzmann Bennett.

- 1091–1100 **The temperature intervals with global exchange of replicas empirical accelerated sampling method: Parameter sensitivity and extension to a complex molecular system**, Xianfeng Li and Robert A. Latour [Clemson University]

The recently developed “temperature intervals with global exchange of replicas” (TIGER2) algorithm is an efficient replica-exchange sampling algorithm that provides the freedom to specify the number of replicas and temperature levels independently of the size of the system and temperature range to be spanned, thus making it particularly well suited for sampling molecular systems that are considered to be too large to be sampled using conventional replica exchange methods. We evaluated the influence of factors such as temperature range, temperature spacing, replica number, and sampling cycle design on the accuracy of a TIGER2 simulation based on molecular dynamics simulations of alanine dipeptide in implicit solvent.

- 1101–1112 **Adsorption and dissociation of NH₃ on clean and hydroxylated TiO₂ rutile (110) surfaces: A computational study**, Jee-Gong Chang [National Center for High-Performance Computing, Tainan], Hsin-Tsung Chen, Shin-Pon Ju, Ching-Sheng Chang and Meng-Hsiung Weng

The adsorption and dissociation of NH₃ on the clean and hydroxylated TiO₂ rutile (110) surfaces have been investigated by the first-principles calculations.

- 1113–1116 **Protein inherent structures by different minimization strategies**, Francesco Rao [University of Freiburg]

See Applications / Free energy calculations.

- 1117–1127 **Inter- and intramolecular dispersion interactions**, Marcel Swart [Universitat de Girona], Miquel Solà and F. Matthias Bickelhaupt

We have investigated the performance of a variety of density functional methods for weak intra- and intermolecular dispersion interactions.

- 1128–1134 **Three-dimensional visualization of the first hyperpolarizability tensor**, Adam Tuer [University of Toronto], Serguei Krouglov, Richard Cisek, Danielle Tokarz and Virginijus Barzda

With polarization dependent second harmonic generation (SHG) microscopy becoming a more popular method for investigating the structure of biological materials, there is a need to develop tools with which to understand and interpret the observed SHG properties. Visualization of the full hyperpolarizability tensor, termed the unit sphere representation, has been developed to provide insight and intuition on the relationship between SHG properties and molecules.

- 1135–1143 **Extending fragment-based free energy calculations with library monte carlo simulation: Annealing in interaction space**, Steven Lettieri, Artem B. Mamonov and Daniel M. Zuckerman [University of Pittsburgh]

See Applications / Free energy calculations.

- 1144–1158 **Electronic structure and relative stability of 1:1 Cu-O₂ adducts from difference-dedicated configuration interaction calculations**, Jhon Zapata-Rivera, Rosa Caballol and Carmen J. Calzado [Universidad de Sevilla]

A computational strategy to analyze Cu-O₂ adducts based on the use of difference-dedicated configuration interaction (DDCI) calculations is presented.

- 1159–1169 **Internucleotide J-couplings and chemical shifts of the N—H...N hydrogen-bonds in the radiation-damaged guanine-cytosine base pairs**, Huifang Li, Laibin Zhang, Li Han, Wenming Sun and Yuxiang Bu [Shandong University]

See Applications / Nucleic Acids.

- 1170–1177 **Mechanism of methylacetylene bisselenation catalyzed by palladium complex from density functional study**, Meiyang Wang, Lin Cheng, Jinping Wang and Zhijian Wu [Chinese Academy of Sciences]

The reaction mechanism of Pd(0)-catalyzed methylacetylene bisselenation reaction is investigated by using the density functional method.

- 1178–1182 **Spin-driven activation of dioxygen in various metalloenzymes and their inspired models**, Aurelien De La Lande [University of Calgary], Dennis R. Salahub, Jacques Maddaluno, Anthony Scemama, Julien Pilme, Olivier Parisel, Helene Gerard, Michel Caffarel and Jean-Philip Piquemal

Although potentially powerful, molecular oxygen is an inert oxidant due to the triplet nature of its ground state. Therefore, many enzymes use various metal cations (M) to produce singlet active species M_nO_2 . In this communication we investigate the topology of the Electron Localization Function (ELF) within five biomimetic complexes which are representative of the strategies followed by metalloenzymes to activate O_2 . We suggest that enzymes could resort to spin state control to tune the regioselectivity of substrate oxidations.

Journal of Molecular Modeling, 17(3), March, 2011.

- 415-422 **Ab initio studies on the decomposition kinetics of CF₃OCF₂O radical**, Hari Ji Singh [DDU Gorakhpur University] and Bhupesh Kumar Mishra

The present study deals with the decomposition of CF₃OCF₂O radical formed from a hydrofluoroether, CF₃OCHF₂ (HFE-125), in the atmosphere.

- 423-428 **Near-field enhancement of infrared intensities for f-f transitions in Er³⁺ ions close to the surface of silicon nanoparticles**, Lesya Borowska, Stephan Fritzsche, Pieter G. Kik and Artëm E. Masunov [University of Central Florida]

Erbium doped waveguide amplifiers can be used in optical integrated circuits to compensate for signal losses. Such amplifiers use stimulated emission from the first excited state ($^4I_{13/2}$) to the ground state ($^4I_{15/2}$) of Er³⁺ at 1.53 μ m, the standard wavelength for optical communication. Here we investigate the effect of the Si nanocluster on the Er³⁺ emission using ab initio theory for the first time.

- 429-442 **Metals in proteins: cluster analysis studies**, Juan A. C. Tamames and Maria João Ramos [Universidade do Porto]

We have conducted a prospective analysis of the Protein Data Bank in order to study certain constituents of proteins: elements that are neither halogens nor phosphorus nor part of the biological amino acid set. A sample of 5749 structures was analyzed and classified according to the 56 elements encountered.

- 443-464 **Discovery of new β -D-glucosidase inhibitors via pharmacophore modeling and QSAR analysis followed by in silico screening**, Reema Abu Khalaf, Ahmed Mutanabbi Abdula, Mohammad S. Mubarak and Mutasem O. Taha [University of Jordan]

See Applications / QSAR.

- 465-475 **Antitumor activity of bent metallocenes: electronic structure analysis using DFT computations**, Dhurairajan Senthilnathan, Sundararajan Vaideeswaran, Ponnambalam Venuvanalingam [Bharathidasan University] and Gernot Frenking

See Methodology / QM and QM/MM.

- 477-493 **Insights into subtype selectivity of opioid agonists by ligand-based and structure-based methods**, Jianxin Cheng, Guixia Liu, Jing Zhang, Zhejun Xu and Yun Tang [East China University of Science and Technology]

See Methodology / Ligand Docking.

- 495-503 **Computational simulations of structural role of the active-site W374C mutation of acetyl-coenzyme-A carboxylase: Multi-drug resistance mechanism**, Xiao-Lei Zhu, Wen-Chao Yang, Ning-Xi Yu, Sheng-Gang Yang and Guang-Fu Yang [Central China Normal University]

See Applications / Medicinal Chemistry and Drug Design.

- 505-514 **The adsorption of mercury-species on relaxed and rumpled CaO (0 0 1) surfaces investigated by density functional theory**, Paul Blowers [The University of Arizona] and Bo Gyeong Kim

This research examines the importance of several computational choices in modeling mercury species adsorption on calcium oxide surfaces and is the second in a series of papers.

- 515-526 **Molecular dynamics studies of the 3D structure and planar ligand binding of a quadruplex dimer**, Ming-Hui Li, Quan Luo, Xiang-Gui Xue and Ze-Sheng Li [Jilin University]

See Applications / QSAR.

- 527-531 **A computational study of atomic oxygen-doped silicon carbide nanotubes**, Maryam Mirzaei and Mahmoud Mirzaei [Islamic Azad University]

See Applications / Carbon Nanotubes.

- 533-541 **Structural and docking studies of Leucaena leucocephala Cinnamoyl CoA reductase**, Nirmal K. Prasad [Goa University], Vaibhav Vindal, Vikash Kumar, Ashish Kabra and Navneet Phogat, et al.

See Applications / Enzyme Catalysis.

- 543-553 **Molecular modeling of lanthionine synthetase component C-like protein 2: a potential target for the discovery of novel type 2 diabetes prophylactics and therapeutics**, Pinyi Lu, David R. Bevan, Stephanie N. Lewis, Raquel Hontecillas and Josep Bassaganya-Riera [Virginia Polytechnic Institute and State University]

See Applications / Homology Modeling.

- 555-564 **Molecular trigger for pre-transfer editing pathway in Valyl-tRNA synthetase: A molecular dynamics simulation study**, Li Li, Long Yu and Qiang Huang [Fudan University]

See Applications / Protein Dynamics.

- 565-572 **Natural bond orbital approach to the transmission of substituent effect through the fulvene and benzene ring systems**, Wojciech P. Oziminski [National Medicines Institute, Chelmska] and Tadeusz M. Krygowski

Electronic structure of 22 monosubstituted derivatives of benzene and exocyclically substituted fulvene with substituents: B(OH)₂, BH₂, CCH, CF₃, CH₃, CHCH₂, CHO, Cl, CMe₃, CN, COCH₃, CONH₂, COOH, F, NH₂, NMe₂, NO, NO₂, OCH₃, OH, SiH₃, SiMe₃ were studied theoretically by means of Natural Bond Orbital analysis.

Molecular Simulation, 37(3), 2011.

- 172 – 195 **Interfacial water on crystalline silica: a comparative molecular dynamics simulation study**, Tuan A. Ho [The University of Oklahoma]; Dimitrios Argyris; Dimitrios V. Papavassiliou; Alberto Striolo; Lloyd L. Lee; David R. Cole

Understanding the properties of interfacial water at solid-liquid interfaces is important in a wide range of applications. Two silica surfaces, with low and high surface hydroxyl density, respectively, were simulated implementing four force fields.

- 196 – 209 **In silico design of potent EGFR kinase inhibitors using combinatorial libraries**, Sisir Nandi [Indian Institute of Chemical Biology]; Manish C. Bagchi

This paper is an attempt to design 4-anilinoquinazoline compounds having promising anticancer activities against epidermal growth factor (EGFR) kinase inhibition, using virtual combinatorial library approach.

- 210 – 225 **Characterisation, applicability and defect analysis for tiles nanostructure of quantum dot cellular automata**, Kunal Das [West Bengal University of Technology]; Debashis De

See Applications / Carbon Nanoparticles.

- 226 – 236 **Structure-based and ligand-based drug design for microsomal prostaglandin E synthase-1 inhibitors**, Chia-Ling Li [China Medical University Hospital]; Tung-Ti Chang; Mao-Feng Sun; Hsin-Yi Chen; Fuu-Jen Tsai; Mark Fisher; Calvin Yu-Chian Chen; Chun-Lin Lee; Wen-Chang Fang; Yung-Hao Wong

See Applications / Medicinal Chemistry and Drug Design.

- 237 – 242 **Mesosopic simulation of aggregate behaviour of fluoropolymers in the TATB-based PBX**, Yanli Zhang [Institute of Fluid Physics, Mianyang]; Guangfu Ji; Feng Zhao; Zizheng Gong; Dongqing Wei; Litao Chen; Wenzhong Li

The aggregate behaviours of fluoropolymers F₂₃₁₁, F₂₃₁₂, F₂₃₁₃ and F₂₃₁₄ in TATB-based PBX were studied using the dissipative particle dynamics method.

- 243 – 249 **Use of sequence-based approach to model and predict the mobile behaviour of peptide cations in ion mobility spectrometry**, Xiangjun Kong [Chongqing University]; Fenglin Lv; Xiaoli Luo; Yuzhu Pan; Bin Wu; Yonggang Ren; Yuanchao Li; Qingwu Yang

A new kind of amino acid descriptors we named integrated property scores (IP scores), were derived from 516 physico-chemical properties using the classical principal component analysis technique, and employed to characterise the sequence pattern profile of 162 single-protonated tripeptides.

- 250 – 256 **Molecular dynamics analysis of potent inhibitors of M2 proton channel against H1N1 swine influenza virus**, Chia-Yu Lai [China Medical University]; Tung-Ti Chang; Mao-Feng Sun; Hsin-Yi Chen; Fuu-Jen Tsai; Jaung-Geng Lin; Calvin Yu-Chian Chen

See Applications / Medicinal Chemmistry and Drug Design.

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1	APPLICATIONS (69)	Page 2		
1.1	Small Molecules (20)			
	Med. Chem. And Drug Design	Page 2	Zeolites	Page 6
	QSAR	Page 5	Carbon Nanoparticles	Page 6
1.2	Biopolymers (49)			
	Bioinformatics and Cheminformatics	Page 7	Ligand Binding	Page 14
	Protein Secondary Structure	Page 8	Enzyme Catalysis	Page 15
	Protein Structure Prediction	Page 9	Protein-Protein Interactions	Page 16
	Comparative or Homology Modeling	Page 9	Membrane Proteins	Page 17
	Protein Conformational Analysis	Page 9	Protein-Nucleic Acids	Page 18
	Protein Dynamics	Page 10	Nucleic Acids	Page 19
	Free Energy Calculations	Page 13		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 20		
2	METHODOLOGY (27)	Page 20		
	QSAR	Page 20	QM & QM/MM	Page 23
	Potentials and Parameters	Page 21	Comparative or Homology	Page 25
	Solvation Energy	Page 22	Ligand Docking	Page 26
	Molecular Dynamics	Page 22		
3	JOURNAL REVIEWS (4)	Page 28		
	Journal of Molecular Graphics and Modeling, 29 (6), April, 2011.			
	Journal of Computational Chemistry, 32 (7), May, 2011.			
	Journal of Molecular Modeling, 17 (4), April, 2011.			
	Molecular Simulation, 37(5), 2011.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 39		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Synthesis, biological evaluation and 3D-QSAR studies of 3-keto salicylic acid chalcones and related amides as novel HIV-1 integrase inhibitors

Horrick Sharma, Shivaputra Patil, Tino W. Sanchez, Nouri Neamati, Raymond F. Schinazi, John K. Buolamwini
[University of Tennessee Health Science Center]

Bioorg. and Med.Chem., **19**, 2030-2045, 2011.

HIV-1 integrase is one of the three most important enzymes required for viral replication and is therefore an attractive target for anti retroviral therapy. We herein report the design and synthesis of 3-keto salicylic acid chalcone derivatives as novel HIV-1 integrase inhibitors. The most active compound, 5-bromo-2-hydroxy-3-[3-(2,3,6-trichlorophenyl)acryloyl]benzoic acid (**25**) was selectively active against integrase strand transfer, with an IC_{50} of 3.7 μ M. This model predicted all the ten compounds of the test set within 0.56 log units of the actual pIC_{50} values; and can be used to guide the rational design of more potent novel 3-keto salicylic acid integrase inhibitors.

A class of novel N-isoquinoline-3-carbonyl-L-amino acid benzylesters: Synthesis, anti-tumor evaluation and 3D QSAR analysis

Meiqing Zheng, Yifan Yang, Ming Zhao, Xiaoyi Zhang, Jianhui Wu, Gong Chen, Li Peng, Yuji Wang, Shiqi Peng
[Capital Medical University]

Europ. Biophys. Jou., **46**, 1672-1681, 2011.

Isoquinoline-3-carboxylic acid (**2**) was modified with amino acid benzylesters and 18 novel N-isoquinoline-3-carbonylamino acid benzylesters (**3a-r**) were provided. The IC_{50} values of **3a-r** against the proliferation of HL-60 and Hela cells were less than 1×10^{-8} M and 6×10^{-7} M, respectively. On S180 mice model 100 μ mol/kg of **3a-r** effectively inhibited the growth of the tumors. Using MFA based Cerius² QSAR module, two equations (r , 0.989 and 0.987) were established to correlate the structure with the in vitro and in vivo activities.



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Medicinal Chemistry and Drug Design (Cont'd)

QSAR study of natural estrogen-like isoflavonoids and diphenolics from Thai medicinal plants

Wanchai De-Eknamkul [Chulalongkorn University], Kaoru Umehara, Orawan Monthakantirat, Radovan Toth, Vladimir Frecer, Lorena Knapic, Paolo Braiuca, Hiroshi Noguchi, Stanislav Miertus

J. Mol.Graph. and Mod., **29**, 784-794, 2011.

Two species of Thai medicinal plants, *Dalbergia parviflora* R. (Leguminosae) and *Belamcanda chinensis* L. (Iridaceae), used traditionally for the regulation of menstrual disorders, have been found to contain a large number of potential estrogen-like compounds. A set of some 55 isolated isoflavonoids and diphenolics showed a wide range of estrogen activity as determined in breast cancer MCF-7 and T47D cell proliferation assays. This set of compounds was studied by means of computational techniques including QSAR and molecular modeling.

Generation and validation of the first predictive pharmacophore model for cyclin-dependent kinase 9 inhibitors

Cheng Fang, Zhiyan Xiao [Chinese Academy of Medical Sciences], Zongru Guo

J. Mol.Graph. and Mod., **29**, 800-808, 2011.

A three-dimensional (3D) pharmacophore modelling approach was applied to a diverse data set of known cyclin-dependent kinase 9 (CDK9) inhibitors. Diversity sampling and principal components analysis (PCA) were employed to ensure the rational selection of representative training sets. Twelve statistically robust pharmacophore models were generated using the HypoGen algorithm. The resulting models showed high homology and indicated great convergence in ascertaining pharmacophoric features essential for CDK9 inhibitory activity.

Computer-aided molecular design of 1H-imidazole-2,4-diamine derivatives as potential inhibitors of Plasmodium falciparum DHFR enzyme

Legesse Adane and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Mod., **17**, 657-667, 2011.

Design and discovery of new potential inhibitors of *Plasmodium falciparum* dihydrofolate reductase (PfDHFR), equally active against both the wild-type and mutant strains, is urgently needed. In this study, a computer-aided molecular design approach that involved ab initio molecular orbital and density functional theory calculations, along with molecular electrostatic potential analysis, and molecular docking studies was employed to design 15 1H-imidazole-2,4-diamine derivatives as potential inhibitors of PfDHFR enzyme.

Molecular dynamics investigation of psalmoepotoxin I. Probing the relationship between 3D structure, anti-malarial activity and thermal stability

Matthew Paul Gleeson [Kasetsart University], Songpon Deechongkit and Somsak Ruchirawat

J. Mol.Mod., **17**, 769-775, 2011.

PcFK1 is a member of the cysteine knot inhibitor family that displays anti-malarial properties. Recent experimental studies on PcFK1 wild-type and mutants, where the cysteine residues of each disulfide bond were mutated into serine residues, suggest that alterations to these structural constraints can give rise to sizeable differences in SAR. To better understand the relationship between the dynamic inhibitor 3D structure, biophysical and biological properties we have performed solution based MD calculations over 150ns using the CHARMM forcefield.

Medicinal Chemistry and Drug Design (Cont'd)

Studying the mechanism that enables paullones to selectively inhibit glycogen synthase kinase 3 rather than cyclin-dependent kinase 5 by molecular dynamics simulations and free-energy calculations

Quan Chen, Wei Cui, Yuanhua Cheng, Fushi Zhang and Mingjuan Ji [Graduate University of Chinese Academy of Sciences]

J. Mol.Mod., **17**, 795-803, 2011.

Glycogen synthase kinase 3 (GSK-3) is an attractive target for the treatment of diabetes, and paullones have been reported to be effective inhibitors of GSK-3. However, it is still a challenging task to improve selectivity among protein kinases, especially cyclin-dependent kinases (CDKs). Here we investigated the mechanism that enables paullones to selectively inhibit GSK-3 rather than cyclin-dependent kinase 5 (CDK5) using sequence alignment, molecular dynamics simulations, free-energy calculations and free-energy decomposition analysis.

Relationship between mutation of serine residue at 315th position in *M. tuberculosis* catalase-peroxidase enzyme and Isoniazid susceptibility: An in silico analysis

Rituraj Purohit, Vidya Rajendran and Rao Sethumadhavan [Vellore Institute of Technology University]

J. Mol.Mod., **17**, 869-877, 2011.

Remarkable advances have been made in the drug therapy of tuberculosis. However much remains to be learned about the molecular and structural basis of drug resistance in *Mycobacterium tuberculosis*. It is known that, activation of Isoniazid (INH) is mediated by *Mycobacterium tuberculosis* catalase-peroxidase (MtBKatG) and mutation at position 315 (serine to threonine) leads to resistance. We have conducted studies on the drug resistance through docking and binding analysis supported by time-scale (~1000 ps) and unrestrained all-atom molecular dynamics simulations of wild and mutant MtBKatG.

Molecular Dynamics Simulation, Free Energy Calculation and Structure-Based 3D-QSAR Studies of B-RAF Kinase Inhibitors

Ying Yang, Jin Qin, Huanxiang Liu, and Xiaojun Yao [Lanzhou University]

J.Chem. Infor. and Mod. **51**, 680–692, 2011.

V^{600E}B-RAF kinase is the most frequent onco-genic protein kinase mutation in melanoma and is a promising target to treat malignant melanoma. In this work, a molecular modeling study combining QM-polarized ligand docking, molecular dynamics, free energy calculation, and three-dimensional quantitative structure–activity relationships (3D-QSAR) was performed on a series of pyridoimidazolone compounds as the inhibitors of V^{600E}B-RAF kinase to understand the binding mode between the inhibitors and V^{600E}B-RAF kinase and the structural requirement for the inhibiting activity.

Computational Studies of the Luciferase Light-Emitting Product: Oxyluciferin

Luis Pinto da Silva and Joaquim C.G. Esteves da Silva [Universidade do Porto]

J. Chem. Theor. and Comp., **7**, 809–817, 2011.

Firefly luciferase is the most studied bioluminescence system, and its catalyzed reactions have been relatively well characterized. However, the color tuning mechanism that leads to firefly multicolor bioluminescence is still unknown, nor is consensual which is the yellow-green and red emitters. Computational studies have been essential in the study of oxyluciferin (OxyLH₂) chemi- and bioluminescence and are responsible for most of our knowledge of this natural phenomenon.

Quantitative Structure-Activity Relations

In vitro and QSAR studies of cucurbitacins on HepG2 and HSC-T6 liver cell lines

Judit Bartalis, Fathi T. Halaweish [SDSU, Shepard Hall 121, Brookings]

Bioorg. and Med.Chem., **19**, 2757-2766, 2011.

The aim of this study was to evaluate cucurbitacins (Cucs) liver protective activity in vitro and conduct QSAR studies against lipophilicity and ab initio descriptors. Nine Cucs were isolated from Cucurbitaceae plants and eight prepared by C2-alkylation or C16-acylation. Ten Cucs demonstrated protective activity on human hepatocyte-derived HepG2 cells exposed to CCl₄ (EC₅₀ = 2.4–45.3 μM) with good margin to toxicity (T/A). All Cucs exhibited anti-proliferative effect on serum-activated rat stellate cells, HSC-T6 (EC₅₀ = 0.02–4.12 μM) with high T/A.

Knowledge-based computational methods for identifying or designing novel, non-homologous antimicrobial peptides

Davor Juretić [University of Split], Damir Vukičević, Dražen Petrov, Mario Novković and Viktor Bojović, et al.

Europ. Biophys. Jou., **40**, 371-385, 2011.

We describe computational approaches for identifying promising lead candidates for the development of peptide antibiotics, in the context of quantitative structure–activity relationships (QSAR) studies for this type of molecule. A first approach deals with predicting the selectivity properties of generated antimicrobial peptide sequences in terms of measured therapeutic indices (TI) for known antimicrobial peptides (AMPs). Based on a training set of anuran AMPs, the concept of sequence moments was used to construct algorithms that could predict TIs for a second test set of natural AMPs and could also predict the effect of point mutations on TI values.

Structure–Activity Relationships of an Antimicrobial Peptide Plantaricin S from Two-Peptide Class IIb Bacteriocins

Wael Soliman, Liru Wang, Subir Bhattacharjee, and Kamaljit Kaur [University of Alberta]

J.Med.Chem. **54**, 2399–2408, 2011.

Class IIb bacteriocins are ribosomally synthesized antimicrobial peptides comprising two different peptides synergistically acting in equal amounts for optimal potency. In this study, we demonstrate for the first time potent (nanomolar) antimicrobial activity of a representative class IIb bacteriocin, plantaricin S (PIs), against four pathogenic Gram-positive bacteria, including *Listeria monocytogenes*. The structure–activity relationships for PIs were studied using activity assays, circular dichroism (CD), and molecular dynamics (MD) simulations.

Discovery of new renin inhibitory leads via sequential pharmacophore modeling, QSAR analysis, in silico screening and in vitro evaluation

Afaf H. Al-Nadaf, Mutasem O. Taha [Applied Science University]

J. Mol.Graph. and Mod., **29**, 843-864, 2011.

The renin–angiotensin–aldosterone system is a major target for the clinical management of hypertension. Development of renin inhibitors has proven to be problematic due to poor bioavailability and complex synthesis. In this study, we combined pharmacophore modeling and quantitative structure–activity relationship (QSAR) analysis to explore the structural requirements for potent renin inhibitors employing 119 known renin ligands.

Quantitative Structure-Activity Relations (Cont'd)

Isolation, biological evaluation and 3D-QSAR studies of insecticidal/narcotic sesquiterpene polyol esters

Shao-peng Wei, Zhi-qin Ji, Hui-xiao Zhang, Ji-wen Zhang and Yong-hua Wang [Northwest Agricultural & Forestry University], et al.

J. Mol.Mod., **17**, 681-693, 2011.

For the first time, a set of (43) natural sesquiterpene polyol esters isolated from the root bark of *Celastrus angulatus* Maxim and *Euonymus japonicus* Thunb were subjected to 3D-QSAR comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) studies, with the aim of proposing novel sesquiterpene-based compounds with optimal narcotic or insecticidal activities. The findings may have valuable implications for the development of novel natural insecticides.

Computational Prediction of Structure-Activity Relationships for the Binding of Aminocyclitols to β -Glucocerebrosidase

Lucia Diaz, Jordi Bujons, Antonio Delgado, Hugo Gutierrez-de-Teran, and Johan Åqvist [Uppsala University]

J.Chem. Infor. and Mod. **51**, 601–611, 2011.

Glucocerebrosidase (GCase, acid β -Glucosidase) hydrolyzes the sphingolipid glucosylceramide into glucose and ceramide. Mutations in this enzyme lead to a lipid metabolism disorder known as Gaucher disease. The design of competitive inhibitors of GCase is a promising field of research for the design of pharmacological chaperones as new therapeutic agents. Using a series of recently reported molecules with experimental binding affinities for GCase in the nanomolar to micromolar range, we here report an extensive theoretical analysis of their binding mode.

Zeolites

Zeolitic imidazolate framework-8 as a reverse osmosis membrane for water desalination: Insight from molecular simulation

Zhongqiao Hu [National University of Singapore], Yifei Chen, and Jianwen Jiang

Jou. Chem. Phys., **134**, 134705, 2011.

A molecular simulation study is reported for water desalination in zeolitic imidazolate framework-8 (ZIF-8) membrane. The simulation demonstrates that water desalination occurs under external pressure, and Na^+ and Cl^- ions cannot transport across the membrane due to the sieving effect of small apertures in ZIF-8. The flux of water permeating the membrane scales linearly with the external pressure, and exhibits an Arrhenius-type relation with temperature (activation energy of 24.4 kJ/mol).

Carbon Nanoparticles

Covalent hybridization of CNT by thymine and uracil: A computational study

Mahmoud Mirzaei, Hamid R. Kalhor and Nasser L. Hadipour [Tarbiat Modares University]

J. Mol.Mod., **17**, 695-699, 2011.

We have investigated the electronic and structural properties of covalent functionalization of the tip of (5,0) carbon nanotube (CNT) by di-keto and keto-enol forms of thymine (T) and uracil (U) nucleobases. Density functional theory (DFT) calculations have been performed to optimize the investigated structures and to calculate the properties such as dipole moment, bond length, band gap, total energy, binding energy and quadrupole coupling constant.

Carbon Nanoparticles (Cont'd)

Predicting helium and neon adsorption and separation on carbon nanotubes by Monte Carlo simulation

Zabiollah Bolboli Nojini [Shahid Chamran University], Amir Abbas Rafati, Seyed Majid Hashemianzadeh and Sepideh Samiee

J. Mol.Mod., **17**, 785-794, 2011.

The adsorption of helium and neon mixtures on single-walled carbon nanotubes (SWCNTs) was investigated at various temperatures (subcritical and supercritical) and pressures using canonical Monte Carlo (CMC) simulation. Adsorption isotherms were obtained at different temperatures (4, 40, 77 and 130 K) and pressures ranging from 1 to 16 MPa. Separation factors and isosteric enthalpies of adsorption were also calculated. Moreover, the adsorption isotherms were obtained at constant specific temperatures (4 and 40 K) and pressures (0.2 and 1.0 MPa) as a function of the amount adsorbed.

Protein stability at a carbon nanotube interface

S. Vaitheeswaran [Rensselaer Polytechnic Institute] and A. E. Garcia

Jou. Chem. Phys., **134**, 125101, 2011.

The interactions of proteins with solid surfaces occur in a variety of situations. Motivated by the many nanoengineering applications of protein-carbon nanotube hybrids, we investigate the conformational transitions of hen egg white lysozyme adsorbed on a carbon nanotube. Using a C_α structure-based model and replica exchange molecular dynamics, we show how the folding/unfolding equilibrium of the adsorbed protein varies with the strength of its coupling to the surface.

1.2. Biopolymers

Bioinformatics and Cheminformatics

birgHPC: creating instant computing clusters for bioinformatics and molecular dynamics

Teong Han Chew, Kwee Hong Joyce-Tan, Farizuwana Akma, and Mohd Shahir Shamsir [Universiti Teknologi Malaysia]

Bioinformatics. **27**, 1320-1321, 2011.

birgHPC, a bootable Linux Live CD has been developed to create high-performance clusters for bioinformatics and molecular dynamics studies using any Local Area Network (LAN)-networked computers. birgHPC features automated hardware and slots detection as well as provides a simple job submission interface. The latest versions of GROMACS, NAMD, mpiBLAST and ClustalW-MPI can be run in parallel by simply booting the birgHPC CD or flash drive from the head node, which immediately positions the rest of the PCs on the network as computing nodes.

Bioinformatics and Cheminformatics (Cont'd)

Rigid substructure search

David Shirvanyants, Anastassia N. Alexandrova, and Nikolay V. Dokholyan [University of North Carolina at Chapel Hill]

Bioinformatics, **27**, 1327-1329, 2011.

Identifying the location of binding sites on proteins is of fundamental importance for a wide range of applications, including molecular docking, de novo drug design, structure identification and comparison of functional sites. Here we present Erebus, a web server that searches the entire Protein Data Bank for a given substructure defined by a set of atoms of interest, such as the binding scaffolds for small molecules. The identified substructure contains atoms having the same names, belonging to same amino acids and separated by the same distances (within a given tolerance) as the atoms of the query structure.

An inverse docking approach for identifying new potential anti-cancer targets

Sam Z. Grinter, Yayun Liang, Sheng-You Huang, Salman M. Hyder, Xiaoqin Zou [University of Missouri]

J. Mol. Graph. and Mod., **29**, 795-799, 2011.

Inverse docking is a relatively new technique that has been used to identify potential receptor targets of small molecules. Our docking software package MDock is well suited for such an application as it is both computationally efficient, yet simultaneously shows adequate results in binding affinity predictions and enrichment tests. As a validation study, we present the first stage results of an inverse-docking study which seeks to identify potential direct targets of PRIMA-1.

Protein Secondary Structure

Rational Design of β -Sheet Ligands Against $A\beta_{42}$ -Induced Toxicity

Katrin Hochdorffer, Julia Marz-Berberich, Luitgard Nagel-Steger, Matthias Eppele, Wolfgang Meyer-Zaika, Anselm H.C. Horn, Heinrich Sticht, Sharmistha Sinha, Gal Bitan, and Thomas Schrader [Universitat Duisburg-Essen]

J. Am. Chem. Soc., **133**, 4348-4358, 2011.

A β -sheet-binding scaffold was equipped with long-range chemical groups for tertiary contacts toward specific regions of the Alzheimer's $A\beta$ fibril. The new constructs contain a trimeric aminopyrazole carboxylic acid, elongated with a C-terminal binding site, whose influence on the aggregation behavior of the $A\beta_{42}$ peptide was studied. MD simulations after trimer docking to the anchor point (F19/F20) suggest distinct groups of complex structures each of which featured additional specific interactions with characteristic $A\beta$ regions.

Alanine-based peptides containing polar residues presumably favour α -helical structure entropically

Wankee Kim [Tokyo University of Science]; Ichiro Yamato; Tadashi Ando

Molecular Simulation, **37**, 379 – 385, 2011.

To evaluate the enthalpic and entropic contributions of polar residues in alanine-based peptides to α -helical propensities of peptides, we applied a Brownian dynamics simulation, together with the umbrella sampling, to two alanine-based 21-residue peptides: one composed of alanine only (AAA), the other composed of 18 alanines and 3 arginines (ARA). Higher α -helical propensity of ARA than that of AAA was obtained.

Protein Structure Prediction

Computational Design of the Sequence and Structure of a Protein-Binding Peptide

Deanne W. Sammond, Dustin E. Bosch, Glenn L. Butterfoss, Carrie Purbeck, Mischa Machius, David P. Siderovski, and Brian Kuhlman [University of North Carolina]

J. Am. Chem. Soc., **133**, 4190–4192, 2011.

The de novo design of protein-binding peptides is challenging because it requires the identification of both a sequence and a backbone conformation favorable for binding. We used a computational strategy that iterates between structure and sequence optimization to redesign the C-terminal portion of the RGS14 GoLoco motif peptide so that it adopts a new conformation when bound to $G\alpha_{i1}$. An X-ray crystal structure of the redesigned complex closely matches the computational model, with a backbone root-mean-square deviation of 1.1 Å.

Comparative or Homology Modeling

Structural and functional studies of a 50 kDa antigenic protein from *Salmonella enterica* serovar Typhi

Yee Siew Choong [Universiti Sains Malaysia, Theam Soon Lim, Ai Lan Chew, Ismail Aziah, Asma Ism]

J. Mol. Graph. and Mod., **29**, 834-842, 2011.

The high typhoid incidence rate in developing and under-developed countries emphasizes the need for a rapid, affordable and accessible diagnostic test for effective therapy and disease management. TYPHIDOT[®], a rapid dot enzyme immunoassay test for typhoid, was developed from the discovery of a ~50 kDa protein specific for *Salmonella enterica* serovar Typhi. This paper described the predictive structure and function of the antigenically specific protein. The homology modeling approach was employed to construct the three-dimensional structure of the antigen.

In Silico sequence analysis and molecular modeling of the three-dimensional structure of DAHP synthase from *Pseudomonas fragi*

Satya Tapas, Girijesh Kumar Patel, Sonali Dhindwal and Shailly Tomar [Indian Institute of Technology, Roorkee]

J. Mol. Mod., **17**, 621-631, 2011.

The shikimate pathway is involved in production of aromatic amino acids in microorganisms and plants. The enzymes of this biosynthetic pathway are a potential target for the design of antimicrobial compounds and herbicides. 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase (DAHPS) catalyzes the first step of the pathway. The three-dimensional structure of Pf-DAHPS was predicted by homology modeling based on the crystal structure of Mt-DAHPS. Pf-DAHPS model contains a $(\beta/\alpha)_8$ TIM barrel structure.

Protein Conformational Analysis

Protein structure predictions by parallel simulated annealing molecular dynamics using genetic crossover

Yoshitake Sakae, Tomoyuki Hiroyasu, Mitsunori Miki and Yuko Okamoto [Nagoya University]

J. Comp. Chem. **32**, 1353–1360, 2011.

We propose a conformational search method to find a global minimum energy structure for protein systems. The simulated annealing is a powerful method for local conformational search. On the other hand, the genetic crossover can search the global conformational space. Our method incorporates these attractive features of the simulated annealing and genetic crossover. In the previous works, we have been using the Monte Carlo algorithm for simulated annealing. In the present work, we use the molecular dynamics algorithm instead.

Protein Dynamics

Protein Shape Change Has a Major Effect on the Gating Energy of a Mechanosensitive Channel

O.H. Samuli Ollila [Tampere University of Technology],
Martti Louhivuori, Siewert J. Marrink, Ilpo Vattulainen

Biophysical Journal. **100**, 1651-1659, 2011.

Increasing experimental evidence has shown that membrane protein functionality depends on molecular composition of cell membranes. Previously it has been demonstrated using models for elastic properties of membranes and lateral pressure profiles of lipid bilayers that the mechanical properties of a lipid bilayer can contribute as much as ~ 10 $k_B T$ to the free energy difference associated with a change in protein conformational state. We use molecular dynamics together with the MARTINI model to simulate the open and closed states of MscL embedded in a DOPC bilayer.

Simulations of allosteric transitions

Ron Elber [The University of Texas at Austin]

Curr. Opin. In Struc. Biol., **21**, 167-172, 2011.

Allosteric transitions are one of the subtler mechanisms used by nature to fine tune protein activity. In this study we consider computational methods for allosteric transitions. We examine accuracy and efficiency of coarse-grained and atomically detailed approaches. We argue that structural features of allosteric pathways can be learned from coarse-grained models. Investigating thermodynamics and kinetics and connecting them to structure require detailed models. Enhanced sampling techniques promise to make detailed calculations a routine.

Advances in all atom sampling methods for modeling protein–ligand binding affinities

Emilio Gallicchio, Ronald M Levy [Rutgers University, Piscataway]

Curr. Opin. In Struc. Biol., **21**, 161-166, 2011.

The aggregation of soluble proteins into fibrillar species is a complex process that spans many lengths and time scales, and that involves the formation of numerous on-pathway and off-pathway intermediate species. Despite this complexity, several elements underlying the aggregation process appear to be universal. We describe coarse-grained computational approaches to model protein aggregation. These models provide insights into the fundamental principles governing aggregation. These models provide new insights into the nucleation and growth phases.

Unfolding the Conformational Behavior of Peptide Dendrimers: Insights from Molecular Dynamics Simulations

Luis C. S. Filipe, Miguel Machuqueiro, and Antonio M. Baptista [Universidade Nova de Lisboa]

J. Am. Chem. Soc., **133**, 5042–5052, 2011.

We present here the first comprehensive structural characterization of peptide dendrimers using molecular simulation methods. Multiple long molecular dynamics simulations are used to extensively sample the conformational preferences of five third-generation peptide dendrimers, including some known to bind aquacobalamine. We start by analyzing the compactness of the conformations thus sampled using their radius of gyration profiles. A more detailed analysis is then performed using dissimilarity measures, principal coordinate analysis, and free energy landscapes, with the aim of identifying groups of similar conformations.

Protein Dynamics (Cont'd)

Monte Carlo study of the molecular mechanisms of surface-layer protein self-assembly

Christine Horejs [University of Natural Resources and Applied Life Sciences], Mithun K. Mitra, Dietmar Pum, Uwe B. Sleytr, and Murugappan Muthukumar

Jou. Chem. Phys., **134**, 125103, 2011.

The molecular mechanisms guiding the self-assembly of proteins into functional or pathogenic large-scale structures can be only understood by studying the correlation between the structural details of the monomer and the eventual mesoscopic morphologies. Using a combination of the structural information and a Monte Carlo method with a coarse-grained model, we have studied the functional protein self-assembly into S(surface)-layers, which constitute the crystallized outer most cell envelope of a great variety of bacterial cells.

Optimizing Protein–Solvent Force Fields to Reproduce Intrinsic Conformational Preferences of Model Peptides

Paul S. Nerenberg and Teresa Head-Gordon [University of California, Berkeley]

J. Chem. Theor. and Comp., **7**, 1220–1230, 2011.

While most force field efforts in biomolecular simulation have focused on the parametrization of the protein, relatively little attention has been paid to the quality of the accompanying solvent model. These considerations are especially relevant for simulations of intrinsically disordered peptides and proteins, for which energy differences between conformations are small and interactions with water are enhanced. In this work, we investigate the accuracy of the AMBER ff99SB force field when combined with the standard TIP3P model or the more recent TIP4P-Ew water model, to generate conformational ensembles for disordered trialanine (Ala₃), triglycine (Gly₃), and trivaline (Val₃) peptides.

Structure and Thermodynamics of Amylin Dimer Studied by Hamiltonian-Temperature Replica Exchange Molecular Dynamics Simulations

Rozita Laghaei, Normand Mousseau [Universite de Montreal], and Guanghong Wei

J. Phys. Chem. B., **115**, 3146–3154, 2011.

The loss of the insulin-producing β -cells in the pancreatic islets of Langerhans, responsible for type-II diabetes, is associated with islet amyloid deposits. In this study, we apply the Hamiltonian-temperature replica exchange molecular dynamics to characterize the structure and thermodynamics of a full-length hIAPP dimer in both the presence and the absence of the Cys2–Cys7 disulfide bond. We compare these results with those obtained on the monomeric and dimeric forms of rat IAPP (rIAPP) with a disulfide bridge which differ from the hIAPP by 6 amino acids in the C-terminal region, but it is unable to form fibrils.

Dynamics of the GB3 Loop Regions from MD Simulation: How Much of It Is Real?

Tong Li, Qingqing Jing, and Lishan Yao [Chinese Academy of Sciences]

J. Phys. Chem. B., **115**, 3488–3495, 2011.

A total of 1.1 μ s of molecular dynamics (MD) simulations were performed to study the structure and dynamics of protein GB3. The simulation motional amplitude of the loop regions is generally overestimated in comparison with the experimental backbone N–H order parameters S^2 . Two-state behavior is observed for several residues in these regions, with the minor state population in the range of 3–13%. Further inspection suggests that the (ϕ , ψ) dihedral angles of the minor states deviate from the GB3 experimental values, implying the existence of nonnative states.

Protein Dynamics (Cont'd)

Regulation of Electron and Proton Transfer by the Protein Matrix of Cytochrome c Oxidase

Vangelis Daskalakis, Stavros C. Farantos, Victor Guallar, and Constantinos Varotsis [Cyprus University of Technology]

J. Phys. Chem. B., **115**, 3648–3655, 2011.

Cytochrome c oxidase (CcO) catalyzes the four-electron reduction of molecular oxygen to water and couples this reduction to the pumping of four protons through the protein matrix. Water molecules inside the protein are involved in the proton pumping activity as proton carriers. Here, we show, by QM/MM simulations, that this conserved water molecule can transfer its proton to propionate-A. By both QM/MM and MD calculations, we demonstrate that the also conserved His403 residue, adjacent to the heme a₃ propionate-A, plays a role of a valve controlling the protonation state of the propionate-A/Asp399 pair.

Molecular dynamics of EF-G during translocation

Wen Li, Leonardo G. Trabuco, Klaus Schulten and Joachim Frank [Columbia University]

Proteins: Stru. Fun. and Bioinfo. **79**, 1478–1486, 2011.

Elongation factor G (EF-G) plays a crucial role in two stages of mRNA-(tRNA)₂ translocation. Many events take place as EF-G undergoes a series of large conformational changes as visualized by cryo-EM and X-ray studies. The number and variety of these structures leave open many questions on how these different configurations form during the dynamic translocation process.

Structural mechanism associated with domain opening in gain-of-function mutations in SHP2 phosphatase

Eva Darian, Olgun Guvench, Bing Yu, Cheng-Kui Qu and Alexander D. MacKerell Jr. [University of Maryland School of Pharmacy]

Proteins: Stru. Fun. and Bioinfo. **79**, 1573–1588, 2011.

The SHP2 phosphatase plays a central role in a number of signaling pathways where it dephosphorylates various substrate proteins. In the present study, a combination of computational and experimental methods are used to investigate the structural mechanism of opening of SHP2 and the impact of three GOF mutants, D61G, E76K, and N308D, on the opening mechanism. Calculated free energies of opening indicate that opening must be facilitated by effector molecules, possibly the protein substrates themselves, as the calculated free energies preclude spontaneous opening.

Mechanism of reactant and product dissociation from the anthrax edema factor: A locally enhanced sampling and steered molecular dynamics study

Leandro Martínez [Universidade de São Paulo], Thérèse E. Malliavin and Arnaud Blondel

Proteins: Stru. Fun. and Bioinfo. **79**, 1649–1661, 2011.

The anthrax edema factor is a toxin overproducing damaging levels of cyclic adenosine mono-phosphate (cAMP) and pyrophosphate (PPi) from ATP. Here, mechanisms of dissociation of ATP and products (cAMP, PPi) from the active site are studied using locally enhanced sampling (LES) and steered molecular dynamics simulations. Various substrate conformations and ionic binding modes found in crystallographic structures are considered. LES simulations show that PPi and cAMP dissociate through different solvent accessible channels, while ATP dissociation requires significant active site exposure to solvent.

Protein Dynamics (Cont'd)

Identification of functional motions in the adenylate kinase (ADK) protein family by computational hybrid approaches

Dagoberto Armenta-Medina, Ernesto Pérez-Rueda and Lorenzo Segovia [Universidad Nacional Autónoma de México]

Proteins: Stru. Fun. and Bioinfo. **79**, 1662–1671, 2011.

Based on integrative computational hybrid approaches that combined statistical coupling analysis (SCA), molecular dynamics (MD), and normal mode analysis (NMA), evolutionarily coupled residues involved in functionally relevant motion in the adenylate kinase protein family were identified. The hybrids identified four top-ranking site pairs that belong to a conserved hydrogen bond network that is involved in the enzyme's flexibility. A second group of top-ranking site pairs was identified in critical regions for functional dynamics, such as those related to enzymatic turnover.

Free Energy Calculations

Efficiency of alchemical free energy simulations. I. A practical comparison of the exponential formula, thermodynamic integration, and Bennett's acceptance ratio method

Stefan Bruckner and Stefan Boresch [University of Vienna]

J. Comp. Chem. **32**, 1303–1319, 2011.

We investigate the relative efficiency of thermodynamic integration, three variants of the exponential formula, also referred to as thermodynamic perturbation, and Bennett's acceptance ratio method to compute relative and absolute solvation free energy differences. Our primary goal is the development of efficient protocols that are robust in practice. We focus on minimizing the number of unphysical intermediate states (λ -states) required for the computation of accurate and precise free energy differences.

Efficiency of alchemical free energy simulations. II. Improvements for thermodynamic integration

Stefan Bruckner and Stefan Boresch [University of Vienna]

J. Comp. Chem. **32**, 1320–1333, 2011.

We attempt to optimize the efficiency of thermodynamic integration, as defined by the minimal number of unphysical intermediate states required for the computation of accurate and precise free energy differences. The suitability of various numerical quadrature methods is tested. In particular, we compare the trapezoidal rule, Simpson's rule, Gauss-Legendre, Gauss-Kronrod-Patterson, and Clenshaw-Curtis integration, as well as integration based on a cubic spline approximation of the integrand.

Analyzing the robustness of the MM/PBSA free energy calculation method: Application to DNA conformational transitions

Allyn R. Brice and Brian N. Dominy [Clemson University]

J. Comp. Chem. **32**, 1431–1440, 2011.

The ability to predict and characterize free energy differences associated with conformational equilibria or the binding of biomolecules is vital to understanding the molecular basis of many important biological functions. The aim of this study is to examine the robustness of the end-point free energy method termed the molecular mechanics Poisson-Boltzmann solvent accessible surface area (MM/PBSA) method. Specifically, applications of MM/PBSA to the conformational equilibria of nucleic acid (NA) systems are explored.

Free Energy Calculations (Cont'd)

Solvation free energies of glutamate and its metal complexes: A computer simulation study

Sepideh Ketabi [Islamic Azad University], Haleh Hashemi Haeri and Seyed Majid Hashemianzadeh

J. Mol. Mod., **17**, 889-898, 2011.

Most biological ion channels demonstrate a high degree of selectivity for one type of ion more than others, and in many cases, how they control attaining this is still not clear. So we have studied on some metal ion compounds of glutamate. The Glutamate and its meal ion compounds (Ca^{2+} , Na^{+} , K^{+} and Li^{+}) were first modeled by ab initio calculations and then Monte Carlo simulation was used to calculate solvation free energies and also the complexes free energies for the related structures.

Global Free Energy Scoring Functions Based on Distance-Dependent Atom-Type Pair Descriptors

Christian Kramer [Novartis Pharma AG] and Peter Gedeck

J.Chem. Infor. and Mod. **51**, 707–720, 2011.

Scoring functions for protein–ligand docking have received much attention in the past two decades. In this study, we analyze how well free energies of binding can be predicted on the basis of crystal structures using traditional QSAR techniques in a proteochemometric approach. We introduce a new set of protein–ligand interaction descriptors on the basis of distance-binned Crippen-like atom type pairs. A subset of the publicly available PDBbind09-CN refined set (MW < 900 g/mol, #P < 2, ndon + nacc < 20; N = 1387) is being used as data set.

Ligand Binding/Docking

Microsecond Simulations Indicate that Ethanol Binds between Subunits and Could Stabilize an Open-State Model of a Glycine Receptor

Samuel Murail, Björn Wallner, James R. Trudell, Edward Bertaccini, Erik Lindahl [Royal Institute of Technology, Stockholm]

Biophysical Journal. **100**, 1642-1650, 2011.

Cys-loop receptors constitute a superfamily of ion channels gated by ligands such as acetylcholine, serotonin, glycine, and γ -aminobutyric acid. All of these receptors are thought to share structural characteristics, but due to high sequence variation and limited structure availability, our knowledge about allosteric binding sites is still limited. We used molecular simulations to study ethanol binding and equilibrium exchange for the homomeric $\alpha 1$ glycine receptor (GlyR $\alpha 1$), modeled on the structure of the *Gloeobacter violaceus* pentameric ligand-gated channel.

A Computational Evaluation of the Mechanism of Penicillin-Binding Protein-Catalyzed Cross-Linking of the Bacterial Cell Wall

Qicun Shi, Samy O. Meroueh, Jed F. Fisher, and Shahriar Mobashery [University of Notre Dame]

J. Am. Chem. Soc., **133**, 5274–5283, 2011.

Penicillin-binding protein 1b (PBP 1b) of the Gram-positive bacterium *Streptococcus pneumoniae* catalyzes the cross-linking of adjacent peptidoglycan strands, as a critical event in the biosynthesis of its cell wall. This enzyme is representative of the biosynthetic PBP structures of the β -lactam-recognizing enzyme superfamily and is the target of the β -lactam antibiotics. The mechanism of this transpeptidation was evaluated using explicit-solvent molecular dynamics simulations and ONIOM quantum mechanics/molecular mechanics calculations.

Ligand Binding / Docking (Cont'd)

In silico analysis of the binding of agonists and blockers to the β_2 -adrenergic receptor

Santiago Vilar, Joel Karpiak, Barkin Berk, Stefano Costanzi
[National Institutes of Health, DHHS]

J. Mol. Graph. and Mod., **29**, 809-817, 2011.

Activation of G protein-coupled receptors (GPCRs) is a complex phenomenon. Here, we applied Induced Fit Docking (IFD) in tandem with linear discriminant analysis (LDA) to generate hypotheses on the conformational changes induced to the β_2 -adrenergic receptor by agonist binding, preliminary to the sequence of events that characterize activation of the receptor. This analysis, corroborated by a follow-up molecular dynamics study, suggested that agonists induce subtle movements to the fifth transmembrane domain (TM5) of the receptor.

Molecular Mechanism of the Affinity Interactions between Protein A and Human Immunoglobulin G1 Revealed by Molecular Simulations

Bo Huang, Fu-Feng Liu, Xiao-Yan Dong, and Yan Sun
[Tianjin University]

J. Phys. Chem. B., **115**, 4168–4176, 2011.

Protein A (SpA) affinity chromatography has been widely used for the purification of immunoglobulin G (IgG). However, the molecular mechanism of the affinity between IgG and SpA remains unclear. In this work, molecular dynamics simulations and molecular mechanics—Poisson–Boltzmann surface area analysis were performed to investigate the molecular mechanism of the affinity interactions. It is found that hydrophobic interaction contributes more than 80% to the binding free energy, while electrostatic interaction plays a minor role (<20%).

Enzyme Catalysis

Computational design of a lipase for catalysis of the Diels-Alder reaction

Mats Linder [Royal Institute of Technology (KTH)], Anders Hermansson, John Liebeschuetz and Tore Brinck

J. Mol. Mod., **17**, 833-849, 2011.

Combined molecular docking, molecular dynamics (MD) and density functional theory (DFT) studies have been employed to study catalysis of the Diels-Alder reaction by a modified lipase. Six variants of the versatile enzyme Candida Antarctica lipase B (CALB) have been rationally engineered in silico based on the specific characteristics of the pericyclic addition. A kinetic analysis reveals that hydrogen bond stabilization of the transition state and substrate binding are key components of the catalytic process.

Allosteric transition and binding of small molecule effectors causes curvature change in central β -sheets of selected enzymes

Ellen Tolonen, Brenda Bueno, Sanjeev Kulshreshta, Piotr Cieplak and Miguel Argáez, Boguslaw Stec [Sanford-Burnham Medical Research Institute], et al.

J. Mol. Mod., **17**, 899-911, 2011.

A quantitative description of allosteric transition remains a significant science challenge. Many allosteric enzymes contain a central β -sheet in their catalytic domain. When an allosteric protein undergoes the transition between T (tense) and R (relaxed) allosteric states, this central β -sheet undergoes a conformational change. We designed a novel quantitative method to demonstrate this conformational transition by measuring the change in curvature of the central β -sheet when enzymes transition between allosteric states. The curvature was established by calculating the semi-axes of a 3-D hyperboloid fitted by least squares to the $\{C\}_{\alpha}$ atomic positions of the β -sheet.

Enzyme Catalysis (Cont'd)

Nature of Allosteric Inhibition in Glutamate Racemase: Discovery and Characterization of a Cryptic Inhibitory Pocket Using Atomistic MD Simulations and pK_a Calculations

Katie L. Whalen, Kenneth B. Tussey, Steven R. Blanke, and M. Ashley Spies [University of Illinois, Urbana]

J. Phys. Chem. B., **115**, 3416–3424, 2011.

Enzyme inhibition via allostery, in which the ligand binds remotely from the active site, is a poorly understood phenomenon and represents a significant challenge to structure-based drug design. Dipicolinic acid (DPA), a major component of *Bacillus* spores, is shown to inhibit glutamate racemase from *Bacillus anthracis*, a monosubstrate/monoproduct enzyme, in a novel allosteric fashion. The DPA binding mode was predicted via multiple docking studies and validated via site-directed mutagenesis at the binding locus, while the mechanism of inhibition was elucidated with a combination of Blue Native polyacrylamide gel electrophoresis, MD simulations, and free energy and pK_a calculations.

Interplay of Flavin's Redox States and Protein Dynamics: An Insight from QM/MM Simulations of Dihydronicotinamide Riboside Quinone Oxidoreductase 2

Robyn M. Mueller, Michael A. North, Chee Yang, Sanchita Hati, and Sudeep Bhattacharyya [University of Wisconsin—Eau Claire]

J. Phys. Chem. B., **115**, 3632–3641, 2011.

Dihydronicotinamide riboside quinone oxidoreductase 2 is known to catalyze a two-electron reduction of quinone to hydroquinone using its cofactor, flavin adenine dinucleotide. Using QM/MM simulations, we have computed the reorganization free energies of the electron and proton transfer processes of flavin in the free state as well as when it is bound in the active site of the enzyme. The calculated energetics for electron transfer processes demonstrate that the enzyme active site lowers the reorganization energy for the redox process as compared to the enzyme-free aqueous state.

Protein-Protein Interactions

Triathlon for energy functions: Who is the winner for design of protein–protein interactions?

Oz Sharabi, Ayelet Dekel and Julia M. Shifman [The Hebrew University of Jerusalem]

Proteins: Stru. Fun. and Bioinfo. **79**, 1487–1498, 2011.

Computational prediction of stabilizing mutations into monomeric proteins has become an almost ordinary task. Yet, computational stabilization of protein–protein complexes remains a challenge. Design of protein–protein interactions (PPIs) is impeded by the absence of an energy function that could reliably reproduce all favorable interactions between the binding partners. In this work, we present three energy functions: one function that was trained on monomeric proteins, while the other two were optimized by different techniques to predict side-chain conformations in a dataset of PPIs.

New benchmark metrics for protein-protein docking methods

Mu Gao and Jeffrey Skolnick [Georgia Institute of Technology]

Proteins: Stru. Fun. and Bioinfo. **79**, 1623–1634, 2011.

With the development of many computational methods that predict the structural models of protein-protein complexes, there is a pressing need to benchmark their performance. Here, we focus on characterizing the similarity of the interfaces of the complex and introduce two scoring functions. The first, the interfacial Template Modeling score (iTM-score), measures the geometric distance between the interfaces, while the second, the Interface Similarity score (IS-score), evaluates their residue-residue contact similarity in addition to their geometric similarity.

Membrane Proteins and Lipid Peptide Interactions

Membrane Interface Composition Drives the Structure and the Tilt of the Single Transmembrane Helix Protein PMP1: MD Studies

Veronica Beswick [Institute of Biology and Technology (iBiTecS), Gif-sur-Yvette], Adriana Isvoran, Pierre Nédellec, Alain Sanson, Nadège Jamin

Biophysical Journal. **100**, 1660-1667, 2011.

PMP1, a regulatory subunit of the yeast plasma membrane H^+ -ATPase, is a single transmembrane helix protein. Its cytoplasmic C-terminus possesses several positively charged residues and interacts with phosphatidylserine lipids as shown through both ^1H - and ^2H -NMR experiments. We used all-atom molecular dynamics simulations to obtain atomic-scale data on the effects of membrane interface lipid composition on PMP1 structure and tilt. PMP1 was embedded in two hydrated bilayers, differing in the composition of the interfacial region.

Lung Surfactant Protein SP-B Promotes Formation of Bilayer Reservoirs from Monolayer and Lipid Transfer between the Interface and Subphase

Svetlana Baoukina, D. Peter Tieleman [University of Calgary]

Biophysical Journal. **100**, 1678-1687, 2011.

We investigated the possible role of SP-B proteins in the function of lung surfactant. To this end, lipid monolayers at the air/water interface, bilayers in water, and transformations between them in the presence of SP-B were simulated. The proteins attached bilayers to monolayers, providing close proximity of the reservoirs with the interface. In the attached aggregates, SP-B mediated establishment of the lipid-lined connection similar to the hemifusion stalk. Via this connection, a lipid flow was initiated between the monolayer at the interface and the bilayer in water in a surface-tension-dependent manner.

Advances in all atom sampling methods for modeling protein–ligand binding affinities

Emilio Gallicchio, Ronald M Levy [Rutgers University, Piscataway]

Curr. Opin. In Struc. Biol., **21**, 161-166, 2011.

Conformational dynamics plays a fundamental role in the regulation of molecular recognition processes. Conformational heterogeneity and entropy variations upon binding, although not always evident from the analysis of structural data, can substantially affect affinity and specificity. Computer modeling is able to provide some of the most direct insights into these aspects of molecular recognition. We review recent physics-based computational studies that employ advanced conformational sampling algorithms and effective potentials to model the three main classes of degrees of freedom relevant to the binding process.

Modeling and simulation of ion-coupled and ATP-driven membrane proteins

José D Faraldo-Gómez, Lucy R Forrest [Max Planck Institute of Biophysics]

Curr. Opin. In Struc. Biol., **21**, 173-179, 2011.

The molecular mechanisms of membrane proteins that are activated either by ions or by ATP are just beginning to come into focus, as long-awaited structural data are revealed. Molecular modeling and simulation provide insights into ion-coupled and ATP-driven membrane proteins. Studies have modeled alternate conformational states and distantly related human homologues. Others identified ion binding sites and explained their selectivity or proposed microscopic mechanisms.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

From Coarse Grained to Atomistic: A Serial Multiscale Approach to Membrane Protein Simulations

Phillip J. Stansfeld and Mark S.P. Sansom [University of Oxford]

J. Chem. Theor. and Comp., **7**, 1157–1166, 2011.

Coarse-grained molecular dynamics provides a means for simulating the assembly and the interactions of membrane protein/lipid complexes at a reduced level of representation, allowing longer and larger simulations. We describe a fragment-based protocol for converting membrane simulation systems, comprising a membrane protein embedded in a phospholipid bilayer, from coarse-grained to atomistic resolution, for further refinement and analysis via atomistic simulations. Overall, this provides a method for generating an accurate and well equilibrated membrane protein/lipid complex.

V GRIFFIN: A Versatile Methodology for Optimization of Protein–Lipid Interfaces for Membrane Protein Simulations

Rene Staritzbichler, Claudio Anselmi, Lucy R. Forrest, and Jose D. Faraldo-Gomez [Max Planck Institute of Biophysics]

J. Chem. Theor. and Comp., **7**, 1167–1176, 2011.

As new atomic structures of membrane proteins are resolved, they reveal increasingly complex transmembrane topologies and highly irregular surfaces with crevices and pores. Here, we introduce GRIFFIN (GRId-based Force Field INput), which uses a versatile framework to automate and improve a widely used membrane-embedding protocol. Initially, GRIFFIN carves out lipid and water molecules from a volume equivalent to that of the protein, to conserve the system density. In the subsequent optimization phase GRIFFIN adds an implicit grid-based protein force field to a MD simulation of the precarved membrane.

Headgroup Mediated Water Insertion into the DPPC Bilayer: A Molecular Dynamics Study

Prithvi Raj Pandey and Sudip Roy [National Chemical Laboratory, Pune]

J. Phys. Chem. B., **115**, 3155–3163, 2011.

Molecular dynamics simulation was performed on the 1,2-dipalmitoyl-sn-phosphocholine (DPPC) bilayer–water system using the GROMOS96 53a6 united atom force field. The transferability of force field was tested by reproducing the area per lipid within 3% accuracy from the experimental value. The simulation shows that water can penetrate much deeper inside the bilayer almost up to the starting point of the aliphatic chain. In this report, for the first time, the mechanism of water insertion deep into the bilayer has been proposed.

Protein-Nucleic acid Interactions

Scoring Function Based Approach for Locating Binding Sites and Understanding Recognition Mechanism of Protein–DNA Complexes

M. Michael Gromiha [Indian Institute of Technology Madras] and Kazuhiko Fukui

J. Chem. Infor. and Mod., **51**, 721–729, 2011.

Protein–DNA recognition plays an essential role in the regulation of gene expression. Understanding the recognition mechanism of protein–DNA complexes is a challenging task in molecular and computational biology. In this work, a scoring function based approach has been developed for identifying the binding sites and delineating the important residues for binding in protein–DNA complexes. This approach considers both the repulsive interactions and the effect of distance between atoms in protein and DNA. The results showed that positively charged, polar, and aromatic residues are important for binding.

Nucleic Acids

Impact of Arsenic/Phosphorus Substitution on the Intrinsic Conformational Properties of the Phosphodiester Backbone of DNA Investigated Using ab Initio Quantum Mechanical Calculations

Elizabeth J. Denning and Alexander D. MacKerell, Jr.
[University of Maryland]

J. Am. Chem. Soc., **133**, 5770–5772, 2011.

Deoxyribonucleic acid (DNA) is composed of five major elements carbon, hydrogen, nitrogen, oxygen, and phosphorus. The substitution of any of these elements in DNA would be anticipated to have major biological implications. However, recent studies have suggested that the substitution of arsenic into DNA (As-DNA) in bacteria may be possible. To help evaluate this possibility, ab initio quantum mechanical calculations are used to show that arsenodiester and phosphodiester linkages have similar geometric and conformational properties.

Dynamical insight into *Caenorhabditis elegans* eIF4E recognition specificity for mono- and trimethylated structures of mRNA 5' cap

Katarzyna Ruszczyńska-Bartnik, Maciej Maciejczyk and Ryszard Stolarski [University of Warsaw]

J. Mol. Mod., **17**, 727–737, 2011.

Specific recognition and binding of the ribonucleic acid 5' termini (mRNA 5' cap) by the eukaryotic translation initiation factor 4E (eIF4E) is a key, rate limiting step in translation initiation. To address the problem of the differences in the mechanism of the cap recognition by those highly homologous proteins, we carried out molecular dynamics simulations in water of three factors, IFE-3 and IFE-5 isoforms from *C. elegans* and murine eIF4E, in the apo form as well as in the complexes with 7-methyl-GDP and N²,N²,7-trimethyl-GDP.

Physics-Based De Novo Prediction of RNA 3D Structures

Song Cao and Shi-Jie Chen [University of Missouri, Columbia]

J. Phys. Chem. B., **115**, 4216–4226, 2011.

Current experiments on structural determination cannot keep up the pace with the steadily emerging RNA sequences and new functions. A recently developed three-vector virtual bond-based RNA folding model ("Vfold") has allowed us to compute the chain entropy and predict folding free energies and structures for RNA secondary structures and simple pseudoknots. Here we develop a free energy-based method to predict larger more complex RNA tertiary folds.

Comparison of Computational Methods to Model DNA Minor Groove Binders

Hemant Kumar Srivastava, Mukesh Chourasia, Devesh Kumar, and G. Narahari Sastry [Indian Institute of Chemical Technology]

J. Chem. Infor. and Mod. **51**, 558–571, 2011.

There has been a profound interest in designing small molecules that interact in sequence-selective fashion with DNA minor grooves. However, most in silico approaches have not been parametrized for DNA ligand interaction. In this regard, a systematic computational analysis of 57 available PDB structures of noncovalent DNA minor groove binders has been undertaken. The study starts with a rigorous benchmarking of GOLD, GLIDE, CDOCKER, and AUTODOCK docking protocols followed by developing QSSR models and finally molecular dynamics simulations.

Surfaces, Catalysts, and Materials Subjects

Self-assembled monolayers of oligosilane on the silicon (001) surface: molecular dynamics simulations

Li Zhao, Xue-Mei Duan, Xiang-Gui Xue, Ming-Hui Li and Ze-Sheng Li [Jilin University]

J. Mol.Mod., **17**, 721-726, 2011.

Atomistic molecular dynamics simulations have been used to investigate the adsorption of permethyldecasilane (MS10) on the silicon (001) surface. The condition under which the self-assembled monolayer forms is examined. The properties of the well-ordered structures, including the packing patterns, the equilibrium distances between two neighboring chains, and the tilt angles, are calculated to characterize the structure of the self-assembled monolayer. The results are comparable with those obtained experimentally.

Molecular dynamics simulations of Nafion and sulfonated polyether sulfone membranes. I. Effect of hydration on aqueous phase structure

Takahiro Ohkubo [National Institute of Advanced Industrial Science and Technology (AIST)], Koh Kidena, Naohiko Takimoto and Akihiro Ohira

J. Mol.Mod., **17**, 739-755, 2011.

We measured the water uptakes and proton conductivities of a Nafion membrane and three sulfonated polyether sulfone membranes (SPEs) with different values of ion-exchange capacity ($IEC = 0.75, 1.0$ and 1.4 meq/g) in relation to relative humidity in order to apply the findings to polymer electrolyte membrane fuel cells. The number of water molecules per sulfonic acid group λ at each humidity level was independent of the relative humidity for all membranes, but the proton conductivities of the SPEs were inferior to that of Nafion for the same λ value. Classical molecular dynamics simulations for the same membranes were carried out using a consistent force field at $\lambda = 3, 6, 9, 12$ and 15 .

2. METHODOLOGY

Quantitative Structure-Activity Relations

Prediction of the PPAR α agonism of fibrates by combined MM-docking approaches

Fabio Lannutti, Alessandro Marrone, Nazzareno Re [Università "G d'Annunzio" di Chieti-Pescara]

J. Mol.Graph. and Mod., **29**, 865-875, 2011.

Fibrates are peroxisome proliferator-activated alpha receptor (PPAR α) activators derived from fibric acid and are the most clinically used therapeutics in the treatment of hypertriglyceridemia. An immense interest for the discovery of new fibrates with improved potency and PPAR α selectivity has stimulated many investigations toward a deeper understanding of structure-activity relationships controlling their activity. The present study aimed at investigating the binding properties of a set of 23 fibrates, characterized by similar carboxylic heads but differing in the size and orientation of the hydrophobic portion, using computational approaches.

Quantitative Structure-Activity Relations (Cont'd)

QSAR-based permeability model for drug-like compounds

Rafael Gozalbes, Mary Jacewicz, Robert Annand, Katya Tsaioun, Antonio Pineda-Lucena [Centro de Investigación Príncipe Felipe (CIPF)]

Bioorg. and Med.Chem., **19**, 2615-2624, 2011.

A QSAR model was developed for predicting intestinal drug permeability, one of the most important parameters when evaluating compounds in drug discovery projects. First, a set of relevant properties for establishing a drug-like chemical space was applied to a database of compounds with Caco-2 permeability values obtained from previous studies. Several QSAR regression models were then developed from this set of drug-like structures.

An accurate nonlinear QSAR model for the antitumor activities of chloroethylnitrosoureas using neural networks

Yu Qin, Hongfei Deng, Hong Yan [Beijing University of Technology], Rugang Zhong

J. Mol.Graph. and Mod., **29**, 826-833, 2011.

The quantitative structure-activity relationship (QSAR) studies are investigated in a series of chloroethylnitrosoureas (CENUs) acting as alkylating agents of tumors by neural networks (NNs). The QSAR model is described inaccurately by the traditional multiple linear regression (MLR) model for the substitution of CENUs at N-3, whose characteristics play key roles in the biological activity. A nonlinear QSAR study is undertaken by a three-layered NN model, using molecular descriptors that are known to be responsible for the antitumor activity to optimize the input variables of the MLR model.

Potentials and Parameters

Combination of the CHARMM27 force field with united-atom lipid force fields

Nicolas Sapay and D. Peter Tieleman [University of Calgary]

J. Comp. Chem. **32**, 1400-1410, 2011.

Computer simulations offer a valuable way to study membrane systems, from simple lipid bilayers to large transmembrane protein complexes and lipid-nucleic acid complexes for drug delivery. We have implemented the widely used CHARMM22 and CHARMM27 force fields in the GROMACS simulation package to (i) combine the CHARMM22 protein force field with two sets of united-atom lipids parameters; (ii) allow comparisons of the lipid CHARMM27 force field with other lipid force fields or lipid-protein force field combinations.

Chemical potential perturbation: A method to predict chemical potentials in periodic molecular simulations

Stan G. Moore [Brigham Young University] and Dean R. Wheeler

Jou. Chem. Phys., **134**, 114514, 2011.

A new method, called chemical potential perturbation (CPP), has been developed to predict the chemical potential as a function of density in periodic molecular simulations. The CPP method applies a spatially varying external force field to the simulation, causing the density to depend upon position in the simulation cell. Following equilibration the homogeneous (uniform or bulk) chemical potential as a function of density can be determined relative to some reference state after correcting for the effects of the inhomogeneity of the system.

Solvation Energy

O(NlogN) Continuous electrostatics method for fast calculation of solvation energies of biomolecules

P. O. Fedichev [Quantum Pharmaceuticals], E. G. Getmantsev and L. I. Menshikov

J. Comp. Chem. **32**, 1368–1376, 2011.

We report the development of a new, fast, surface-based method for numerical calculations of the solvation energy of biomolecules with a large number of charged groups. The procedure scales linearly with the system size, both in time and memory requirements, produces explicit values for the reaction field potential and stable values of the polar energy within only a few percent error margin practically for any molecular configurations.

Molecular Dynamics

Calculation of Raman Optical Activity Spectra of Methyl- β -d-Glucose Incorporating a Full Molecular Dynamics Simulation of Hydration Effects

James R. Cheeseman, Majeed S. Shaik, Paul L. A. Popelier, and Ewan W. Blanch [University of Manchester]

J. Am. Chem. Soc., **133**, 4991–4997, 2011.

We report calculations of the Raman and Raman optical activity (ROA) spectra of methyl- β -d-glucose utilizing density functional theory combined with molecular dynamics (MD) simulations to provide an explicit hydration environment. This is the first report of such combination of MD simulations with ROA ab initio calculations. We achieve a significant improvement in accuracy over the more commonly used gas phase and polarizable continuum model (PCM) approaches, resulting in an excellent level of agreement with the experimental spectrum.

In silico prediction of deleterious single amino acid polymorphisms from amino acid sequence

Shuyan Li, Lili Xi, Jiazhong Li, Chengqi Wang, Beilei Lei, Yulin Shen, Huanxiang Liu, Xiaojun Yao [Lanzhou University] and Biao Li

J. Comp. Chem. **32**, 1211–1216, 2011.

Trivial trajectory parallelization of multicanonical molecular dynamics (TTP-McMD) explores the conformational space of a biological system with multiple short runs of McMD starting from various initial structures. This method simply connects (i.e., trivially parallelizes) the short trajectories and generates a long trajectory. First, we theoretically prove that the simple trajectory connection satisfies a detailed balance automatically. Thus, the resultant long trajectory is regarded as a single multicanonical trajectory.

Molecular Dynamics Simulation Study of Chlorophyll a in Different Organic Solvents

Khadga Karki and Danilo Roccatano [Jacobs University Bremen]

J. Chem. Theor. and Comp., **7**, 1131–1140, 2011.

Herein, we present a new model of chlorophyll a for molecular dynamics simulations based on the optimized potentials for liquid simulations force field. The new model was used to study the structural and dynamic properties of the molecule in three different solvents: water, methanol, and benzene. The results of the simulations show that structural and dynamic properties of the chlorin ring are similar in both methanol and benzene.

Molecular Dynamics (Cont'd)

Analysis of Twisting of Cellulose Nanofibrils in Atomistic Molecular Dynamics Simulations

Sami Paavilainen [Tampere University of Technology],
Tomasz Rog, and Ilpo Vattulainen

J. Phys. Chem. B., **115**, 3747–3755, 2011.

We use atomistic molecular dynamics simulations to study the crystal structure of cellulose nanofibrils, whose sizes are comparable with the crystalline parts in commercial nanocellulose. The simulations show twisting, whose rate of relaxation is strongly temperature dependent. Meanwhile, no significant bending or stretching of nanocellulose is discovered. Considerations of atomic-scale interaction patterns bring about that the twisting arises from hydrogen bonding within and between the chains in a fibril.

A Refined, Efficient Mean Solvation Force Model that Includes the Interior Volume Contribution

Jane R. Allison, Katharina Boguslawski, Franca Fraternali,
and Wilfred F. van Gunsteren [Swiss Federal Institute of
Technology]

J. Phys. Chem. B., **115**, 4547–4557, 2011.

A refined implicit aqueous solvation model is proposed for the simulation of biomolecules without the explicit inclusion of the solvent degrees of freedom. The mean force due to solvation is approximated by the derivative of a simple analytic function of the solvent accessible surface area combined with two atomic solvation parameters, as described previously, with the addition of a novel term to account for the interaction of the interior atoms of the solute with the solvent. The mean solvation model proposed here improves the structural properties relative to vacuum simulations and relative to the simpler model that neglects the volume contribution, while remaining significantly more efficient than simulations in explicit water.

QM and QM/MM

QM/MM Study of the Structure, Energy Storage, and Origin of the Bathochromic Shift in Vertebrate and Invertebrate Bathorhodopsins

Sivakumar Sekharan and Keiji Morokuma [Emory University,
Atlanta]

J. Am. Chem. Soc., **133**, 4734–4737, 2011.

By comparing the results from a hybrid quantum mechanics/molecular mechanics method (SORCI+Q//B3LYP/6-31G*:Amber) between vertebrate (bovine) and invertebrate (squid) visual pigments, the mechanism of molecular rearrangements, energy storage, and origin of the bathochromic shift accompanying the transformation of rhodopsin to bathorhodopsin have been evaluated. The analysis reveals that, in the presence of an unrelaxed binding site, bathorhodopsin was found to carry almost 27 kcal/mol energy in both visual pigments and absorb (λ_{max}) at 528 nm in bovine and 554 nm in squid.

QM and QM/MM (Cont'd)

Design Parameters for Tuning the Type 1 Cu Multicopper Oxidase Redox Potential: Insight from a Combination of First Principles and Empirical Molecular Dynamics Simulations

Gongyi Hong, Dmitri M. Ivnitski, Glenn R. Johnson, Plamen Atanasov, and Ruth Pachter [Wright-Patterson Air Force Base]

J. Am. Chem. Soc., **133**, 4802–4809, 2011.

The redox potentials and reorganization energies of the type 1 (T1) Cu site in four multicopper oxidases were calculated by combining first principles density functional theory (QM) and QM/MM molecular dynamics (MD) simulations. The model enzymes selected included the laccase from *Trametes versicolor*, the laccase-like enzyme isolated from *Bacillus subtilis*, CueO required for copper homeostasis in *Escherichia coli*, and the small laccase (SLAC) from *Streptomyces coelicolor*. The results demonstrated good agreement with experimental data and provided insight into the parameters that influence the T1 redox potential.

Can Ferric-Superoxide Act as a Potential Oxidant in P450_{cam}? QM/MM Investigation of Hydroxylation, Epoxidation, and Sulfoxidation

Wenzhen Lai and Sason Shaik [The Hebrew University of Jerusalem]

J. Am. Chem. Soc., **133**, 5444–5452, 2011.

In view of recent reports of high reactivity of ferric-superoxide species in heme and nonheme systems (Morokuma et al. *J. Am. Chem. Soc.* 2010, 132, 11993–12005; Que et al. *Inorg. Chem.* 2010, 49, 3618–3628; Nam et al. *J. Am. Chem. Soc.* 2010, 132, 5958–5959; *J. Am. Chem. Soc.* 2010, 132, 10668–10670), we use herein combined quantum mechanics/molecular mechanics (QM/MM) methods to explore the potential reactivity of P450_{cam} ferric-superoxide toward hydroxylation, epoxidation, and sulfoxidation.

Electronic ground states and vibrational frequency shifts of diatomic ligands in heme adducts

Yang Liu and Huai Sun [Shanghai Jiao Tong University]

J. Comp. Chem. **32**, 1279–1285, 2011.

DFT calculations were carried out to study heme complexes with diatomic ligand (CO, NO, or O₂) and trans-imidazole ligand. The optimized electronic ground states of CO, NO, and O₂ adducts are singlet, doublet, and open-shell singlet, respectively. For O₂ adduct, the open-shell singlet is slightly lower in energy than the close-shell singlet. However, important differences are found in optimized structures and vibrational frequencies. Particularly, the trans-imidazole-induced frequency up-shift of the Fe—O(O) stretching mode can be predicted only with the open-shell singlet as ground state.

Insight into analysis of interactions of GW9508 to wild-type and H86F and H137F GPR40: A combined QM/MM study and pharmacophore modeling

Shao-Yong Lu, Yong-Jun Jiang [Zhejiang University, Jian-Wei Zou, Hai-Bin Luo, Tian-Xing Wu]

J. Mol. Graph. and Mod., **29**, 818–825, 2011.

GPR40 is a novel potential target for the treatment of type 2 diabetes. In this work, a two-layered ONIOM based QM/MM approach was employed to study the interactions between GW9508 and GPR40: wild-type, H86F, and H137F mutated systems. The calculated results clearly indicated that His137 is directly involved in ligand recognition through the NH– π interaction with the GW9508. In contrast, His86 is not interacting with the GW9508 in the NH– π interaction.

QM and QM/MM (Cont'd)

Ab Initio QM/MM Free-Energy Studies of Arginine Deiminase Catalysis: The Protonation State of the Cys Nucleophile

Zhihong Ke and Hua Guo [University of New Mexico] ,
Daiqian Xie , Shenglong Wang and Yingkai Zhang

J. Phys. Chem. B., **115**, 3725–3733, 2011.

The first step of the hydrolytic deimination of l-arginine catalyzed by arginine deiminase is examined using ab initio quantum mechanical/molecular mechanical molecular dynamics simulations. Two possible protonation states of the nucleophilic Cys406 residue were investigated, and the corresponding activation free energies were obtained via umbrella sampling. Our calculations indicated a reaction free-energy barrier of 21.3 kcal/mol for the neutral cysteine, which is in reasonably good agreement with the experimental k_{cat} value of 6.3 s^{-1} , i.e., a barrier of 16.7 kcal/mol.

Enhancing QM/MM Molecular Dynamics Sampling in Explicit Environments via an Orthogonal-Space-Random-Walk-Based Strategy

Donghong Min, Mengen Chen, Lianqing Zheng, Yonghao Jin, Martin A. Schwartz, Qing-Xiang Amy Sang, and Wei Yang [Florida State University, Tallahassee]

J. Phys. Chem. B., **115**, 3924–3935, 2011.

Accurate prediction of molecular conformations in explicit environments, such as aqueous solution and protein interiors, can facilitate our understanding of various molecular recognition processes. Taking advantage of a recent second-order generalized ensemble scheme [e.g., the orthogonal space random walk (OSRW) strategy], which can synergistically accelerate the motion of a focused region and its coupled environmental response, we are presenting a QM/MM based molecular dynamics sampling technique to explore molecular conformational landscapes in explicit environments.

Comparative or Homology Modeling

New Insights into the Binding Mode of Melanin Concentrating Hormone Receptor-1 Antagonists: Homology Modeling and Explicit Membrane Molecular Dynamics Simulation Study

Mohamed A. Helal, Amar G. Chittiboyina, and Mitchell A. Avery [University of Mississippi]

J.Chem. Infor. and Mod. **51**, 635–646, 2011.

Melanin concentrating hormone (MCH) is a cyclic 19-amino-acid peptide expressed mainly in the hypothalamus. Administration of MCH-R1 antagonists has been proved to reduce food intake and cause weight loss in animal models. In the present study, a homology model of the human MCH-R1 was constructed using the crystal structure of bovine rhodopsin (PDB: 1u19) as a template. Based on the observation that MCH-R1 can bind ligands of high chemical diversity, the initial model was subjected to an extensive ligand-supported refinement using antagonists of different chemotypes.

Computational prediction and analysis of the DR6–NAPP interaction

Sergei Y. Ponomarev and Joseph Audie [Sacred Heart University]

Proteins: Stru. Fun. and Bioinfo. **79**, 1376–1395, 2011

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that involves a devastating clinical course and that lacks an effective treatment. we used a pure computational work-flow to dock a binding competent homology model of the DR6 ectodomain to a binding competent crystal structure of GFD NAPP. The DR6 homology model was built according to a template supplied by the neurotrophin p75 receptor. The best docked model was selected according to an empirical estimate of the binding affinity and represents a high quality model of probable structural accuracy, especially with respect to the residue-level contribution of GFD NAPP.

Comparative / Homology Modeling (Cont'd)

Modeling GPCR active state conformations: The β_2 -adrenergic receptor

Lisa M. Simpson, Ian D. Wall, Frank E. Blaney and Christopher A. Reynolds [University of Essex]

Proteins: Stru. Fun. and Bioinfo. **79**, 1441–1457, 2011.

The recent publication of several G protein-coupled receptor (GPCR) structures has increased the information available for homology modeling inactive class A GPCRs. Moreover, the opsin crystal structure shows some active features. We have therefore combined information from these two sources to generate an extensively validated model of the active conformation of the β_2 -adrenergic receptor. Experimental information on fully active GPCRs from zinc binding studies, site-directed spin labeling, and other spectroscopic techniques has been used in molecular dynamics simulations.

Ligand Docking

BINANA: A novel algorithm for ligand-binding characterization

Jacob D. Durrant [University of California San Diego], J. Andrew McCammon

J. Mol.Graph. and Mod., **29**, 888-893, 2011.

Computational chemists and structural biologists are often interested in characterizing ligand–receptor complexes for hydrogen-bond, hydrophobic, salt-bridge, van der Waals, and other interactions in order to assess ligand binding. When done by hand, this characterization can become tedious, especially when many complexes need be analyzed. In order to facilitate the characterization of ligand binding, we here present a novel Python-implemented computer algorithm called BINANA (BINDing ANALyzer), which is freely available for download at <http://www.nbcr.net/binana/>. To demonstrate the utility of the new algorithm, we use BINANA to confirm that the number of hydrophobic contacts between a ligand and its protein receptor is positively correlated with ligand potency.

Design of 1-arylsulfamido-2-alkylpiperazine derivatives as secreted PLA2 inhibitors

Preethi Badrinarayan, P. Srivani and G. Narahari Sastry [Indian Institute of Chemical Technology,Tarnaka]

J. Mol.Mod., **17**, 817-831, 2011.

Structure and analog based analysis of 3D-QSAR, CoMFA and CoMSIA, along with different docking protocols were used to evaluate the structure activity relationship of 26 analogues of 1-aryl sulfamido-2-alkyl piperazines to model the activities of group I and II secreted phospholipases A₂ (sPLA₂s) and probe into the chemical space and nature of receptor — ligand interactions. Molecular modeling studies indicate that the newly designed ligands are expected to show high affinity and experimental efforts in this direction is highly rewarding.

Ligand Docking (Cont'd)

Docking-Based Comparative Intermolecular Contacts Analysis as New 3-D QSAR Concept for Validating Docking Studies and in Silico Screening: NMT and GP Inhibitors as Case Studies

Mutasem O. Taha [University of Jordan], Maha Habash, Zeina Al-Hadidi, Amal Al-Bakri, Khaled Younis, and Suhaib Sisan

J.Chem. Infor. and Mod. **51**, 647–669, 2011.

The significant role played by docking algorithms in drug discovery combined with their serious pitfalls prompted us to envisage a novel concept for validating docking solutions, namely, docking-based comparative intermolecular contacts analysis (dbCICA). This novel approach is based on the number and quality of contacts between docked ligands and amino acid residues within the binding pocket. It assesses a particular docking configuration on the basis of its ability to align a set of ligands within a corresponding binding pocket in such a way that potent ligands come into contact with binding site spots distinct from those approached by low-affinity ligands and vice versa.

Significant Enhancement of Docking Sensitivity Using Implicit Ligand Sampling

Mengang Xu and Markus A. Lill [Purdue University]

J.Chem. Infor. and Mod. **51**, 693–706, 2011.

The efficient and accurate quantification of protein–ligand interactions using computational methods is still a challenging task. Two factors strongly contribute to the failure of docking methods to predict free energies of binding accurately: the insufficient incorporation of protein flexibility coupled to ligand binding and the neglected dynamics of the protein–ligand complex in current scoring schemes. We have developed a new methodology, named the ‘ligand-model’ concept, to sample protein conformations that are relevant for binding structurally diverse sets of ligands.

First Principles-Based Calculations of Free Energy of Binding: Application to Ligand Binding in a Self-Assembling Superstructure

Stephen Fox, Hannes G. Wallnoefer, Thomas Fox, Christofer S. Tautermann, and Chris-Kriton Skylaris [University of Southampton]

J. Chem. Theor. and Comp. **7**, 1102–1108, 2011.

The accurate prediction of ligand binding affinities to a protein remains a desirable goal of computational biochemistry. Many available methods use molecular mechanics (MM) to describe the system, however, MM force fields cannot fully describe the complex interactions involved in binding, specifically electron transfer and polarization. First principles approaches can fully account for these interactions, and with the development of linear-scaling first principles programs, it is now viable to apply first principles calculations to systems containing tens of thousands of atoms.

New insights into the GABA_A receptor structure and orthosteric ligand binding: Receptor modeling guided by experimental data

Tommy Sander, Bente Frølund, Anne Techau Bruun, Ivaylo Ivanov, James Andrew McCammon and Thomas Balle [University of Copenhagen]

Proteins: Stru. Fun. and Bioinfo. **79**, 1458–1477, 2011.

GABA_A receptors (GABA_ARs) are ligand gated chloride ion channels that mediate overall inhibitory signaling in the CNS. A detailed understanding of their structure is important to gain insights in, e.g., ligand binding and functional properties of this pharmaceutically important target. Homology modeling is a necessary tool in this regard because experimentally determined structures are lacking. Here we present an exhaustive approach for creating a high quality model of the $\alpha_1\beta_2\gamma_2$ subtype of the GABA_AR ligand binding domain, and we demonstrate its usefulness in understanding details of orthosteric ligand binding.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 29(6), April, 2011.

- 777-783 **Theoretical investigation of nitric oxide interaction with aluminum phthalocyanine**, Valter H.C. Silva [Unidade Universitária de Ciências Exatas e Tecnológicas], Marcos P. Martins, Heibbe C.B. de Oliveira, Ademir J. Camargo

Nitric oxide (NO) is an extremely toxic compound formed during combustion, predominantly at high temperatures, and it is among the most important atmospheric pollutants. With the aim of developing new materials that can be used as selective chemical sensors or as biomedical NO delivery agents we carried out a quantum mechanical study of the interaction of NO with aluminum phthalocyanine (AlPc) at B3LYP/6-31G* level.

- 784-794 **QSAR study of natural estrogen-like isoflavonoids and diphenolics from Thai medicinal plants**, Wanchai De-Eknamkul [Chulalongkorn University], Kaoru Umehara, Orawan Monthakantirat, Radovan Toth, Vladimir Frecer, Lorena Knapic, Paolo Braiuca, Hiroshi Noguchi, Stanislav Miertus

See Applications / Medicinal Chemistry and Drug Design.

- 795-799 **An inverse docking approach for identifying new potential anti-cancer targets**, Sam Z. Grinter, Yayun Liang, Sheng-You Huang, Salman M. Hyder, Xiaoqin Zou [University of Missouri]

See Applications / Bioinformatics.

- 800-808 **Generation and validation of the first predictive pharmacophore model for cyclin-dependent kinase 9 inhibitors**, Cheng Fang, Zhiyan Xiao [Chinese Academy of Medical Sciences], Zongru Guo

See Applications / Medicinal Chemistry and Drug Design.

- 809-817 **In silico analysis of the binding of agonists and blockers to the β_2 -adrenergic receptor**, Santiago Vilar, Joel Karpiak, Barkin Berk, Stefano Costanzi [National Institutes of Health, DHHS]

See Applications / Ligand Binding.

- 818-825 **Insight into analysis of interactions of GW9508 to wild-type and H86F and H137F GPR40: A combined QM/MM study and pharmacophore modeling**, Shao-Yong Lu, Yong-Jun Jiang [Zhejiang University, Jian-Wei Zou, Hai-Bin Luo, Tian-Xing Wu]

See Methodology / QM and QM/MM.

- 826-833 **An accurate nonlinear QSAR model for the antitumor activities of chloroethylnitrosoureas using neural networks**, Yu Qin, Hongfei Deng, Hong Yan [Beijing University of Technology], Rugang Zhong

See Methodology / QSAR.

- 834-842 **Structural and functional studies of a 50 kDa antigenic protein from *Salmonella enterica* serovar Typhi**, Yee Siew Choong [Universiti Sains Malaysia, Theam Soon Lim, Ai Lan Chew, Ismail Aziah, Asma Ism]

See Applications / Homology Modeling.

- 843-864 **Discovery of new renin inhibitory leads via sequential pharmacophore modeling, QSAR analysis, in silico screening and in vitro evaluation**, Afaf H. Al-Nadaf, Mutasem O. Taha [Applied Science University]

See Applications / QSAR.

- 865-875 **Prediction of the PPAR α agonism of fibrates by combined MM-docking approaches**, Fabio Lannutti, Alessandro Marrone, Nazzareno Re [Università "G d'Annunzio" di Chieti-Pescara]

See Methodology / QSAR.

- 876-887 **Phase-transfer energetics of small-molecule alcohols across the water-hexane interface: Molecular dynamics simulations using charge equilibration models**, Brad A. Bauer, Yang Zhong, David J. Meninger, Joseph E. Davis, Sandeep Patel [University of Delaware]

We study the water-hexane interface using molecular dynamics (MD) and polarizable charge equilibration (CHEQ) force fields.

- 888-893 **BINANA: A novel algorithm for ligand-binding characterization**, Jacob D. Durrant [University of California San Diego], J. Andrew McCammon

See Methodology / Ligand Docking.

Journal of Computational Chemistry, 32(7), May, 2011.

- 1211-1216 **In silico prediction of deleterious single amino acid polymorphisms from amino acid sequence**, Shuyan Li, Lili Xi, Jiazhong Li, Chengqi Wang, Beilei Lei, Yulin Shen, Huanxiang Liu, Xiaojun Yao [Lanzhou University] and Biao Li

Molecular cause of human disease retains as one of the most attractive scientific research targets for decades. An effective approach toward this topic is analysis and identification of disease-related amino acid polymorphisms. In this work, we developed a concise and promising deleterious amino acid polymorphism identification method SeqSubPred based on 44 features solely extracted from protein sequence.

- 1217-1227 **The charge-transfer states in a stacked nucleobase dimer complex: A benchmark study**, Adélia J. A. Aquino, Dana Nachtigallova, Pavel Hobza, Donald G. Truhlar, Christof Hättig and Hans Lischka [University of Vienna]

Electronic singlet excitations of stacked adenine–thymine (AT) and guanine–cytosine (GC) complexes have been investigated with respect to local excitation and charge-transfer (CT) characters.

- 1228–1234 **On easy implementation of a variant of the replica exchange with solute tempering in GROMACS**, Tsuyoshi Terakawa, Tomoshi Kameda and Shoji Takada [Kyoto University]

To reduce the number of replicas required in the conventional replica exchange method for huge systems, recently the replica exchange with solute tempering (REST) method was proposed. Here we showed that a variant of REST realized by rescaling the force-field parameters can be performed with GROMACS 4 without changing the code.

- 1235–1240 **First-principles investigation of A-B intersite charge transfer and correlated electrical and magnetic properties in $\text{BiCu}_3\text{Fe}_4\text{O}_{12}$** , Hongping Li, Shuhui Lv, Xiaojuan Liu and Jian Meng [Chinese Academy of Sciences]

First-principles calculations using the augmented plane wave plus local orbitals method, as implemented in the WIEN2K code, have been carried out to study the A-B intersite charge transfer and the correlated electrical and magnetic properties of the perovskite $\text{BiCu}_3\text{Fe}_4\text{O}_{12}$, especially as regards the charge transfer.

- 1241–1261 **Density functional study of structural, electronic, and optical properties of small bimetallic ruthenium-copper clusters**, Efstathios E. Karagiannis, Christos E. Kefalidis, Ioanna Petrakopoulou and Constantinos A. Tsipis [Aristotle University of Thessaloniki]

The structural, electronic, bonding, magnetic, and optical properties of bimetallic $[\text{Cu}_n\text{Ru}_m]^{+/0/-}$ ($n + m \leq 3$; $n, m = 0-3$) clusters were computed in the framework of the density functional theory (DFT) and time-dependent DFT (TD-DFT) using the full-range PBE0 nonlocal hybrid GGA functional combined with the Def2-QZVPP basis sets.

- 1262–1270 **Fast calculation of DNMR spectra on CUDA-enabled graphics card**, Zsófia Szalay and János Rohonczy [Eötvös Loránd University]

During the past few years, general-purpose graphics processing units (GPGPUs) have become rather popular in the high performance computing community. In this study, we present an implementation of the simulation of dynamic nuclear magnetic resonance (DNMR) spectra.

- 1271–1278 **Competitive diamond-like and endohedral fullerene structures of Si_{70}** , Li-Zhen Zhao, Wan-Sheng Su, Wen-Cai Lu [Qingdao University], C. Z. Wang and K. M. Ho

We performed first-principles calculations to study the structure and stability of Si_{70} cluster. The results from the density functional theory calculation with the Becke–Lee–Yang–Parr and B3LYP exchange-correlation functionals suggest that a diamond-like Si_{70} isomer is the most stable structure, in contrast to endohedral fullerenes of Si_{70} .

- 1279–1285 **Electronic ground states and vibrational frequency shifts of diatomic ligands in heme adducts**, Yang Liu and Huai Sun [Shanghai Jiao Tong University]

See Methodology / QM and QM/MM.

- 1286–1297 **Theory for trivial trajectory parallelization of multicanonical molecular dynamics and application to a polypeptide in water**, Jinzen Ikebe, Koji Umezawa, Narutoshi Kamiya, Takanori Sugihara, Yasushige Yonezawa, Yu Takano, Haruki Nakamura and Junichi Higo [Osaka University]

See Methodology / Molecular Dynamics.

- 1298–1302 **Effect of native defects and Co doping on ferromagnetism in HfO₂: First-principles calculations**, Chong Han, Shi-Shen Yan [Shandong University], Xue-Ling Lin, Shu-Jun Hu, Ming-Wen Zhao, Xin-Xin Yao, Yan-Xue Chen, Guo-Lei Liu and Liang-Mo Mei

First-principles calculations of undoped HfO₂ and cobalt-doped HfO₂ have been carried out to study the magnetic properties of the dielectric material.

- 1303–1319 **Efficiency of alchemical free energy simulations. I. A practical comparison of the exponential formula, thermodynamic integration, and Bennett's acceptance ratio method**, Stefan Bruckner and Stefan Boresch [University of Vienna]

See Applications / Free energy computation.

- 1320–1333 **Efficiency of alchemical free energy simulations. II. Improvements for thermodynamic integration**, Stefan Bruckner and Stefan Boresch [University of Vienna]

See Applications / Free energy computation.

- 1334–1344 **Polarizable protein packing**, Albert H. Ng and Christopher D. Snow [California Institute of Technology]

To incorporate protein polarization effects within a protein combinatorial optimization framework, we decompose the polarizable force field AMOEBA into low order terms. Including terms up to the third-order provides a fair approximation to the full energy while maintaining tractability. We represent the polarizable packing problem for protein G as a hypergraph and solve for optimal rotamers with the FASTER combinatorial optimization algorithm.

- 1345–1352 **A theoretical investigation on optimal structures of ethane clusters (C₂H₆)_n with n ≤ 25 and their building-up principle**, Hiroshi Takeuchi [Hokkaido University]

Geometry optimization of ethane clusters (C₂H₆)_n in the range of n ≤ 25 is carried out with a Morse potential. A heuristic method based on perturbations of geometries is used to locate global minima of the clusters.

- 1353–1360 **Protein structure predictions by parallel simulated annealing molecular dynamics using genetic crossover**, Yoshitake Sakae, Tomoyuki Hiroyasu, Mitsunori Miki and Yuko Okamoto [Nagoya University]

See Applications / Protein Confirmation analysis.

- 1361–1367 **Reexamination of the π -bond strengths within H₂C=XH_n systems: A theoretical study**, Jun-Xian Chen, Chang Kon Kim, Hai Whang Lee, Ying Xue and Chan Kyung Kim [Inha University]

The accurate determination of π -bond energies, D_π , in doubly-bonded species has been an important issue in theoretical chemistry. The aim of this study was to examine whether the procedure could be a reliable methodology for estimating the D_π values for a variety of $H_2C=XH_n$ species.

- 1368–1376 **O(NlogN) Continuous electrostatics method for fast calculation of solvation energies of biomolecules**, P. O. Fedichev [Quantum Pharmaceuticals], E. G. Getmantsev and L. I. Menshikov

See Methodology / Solvation energy.

- 1377–1385 **Composition-induced structural transitions in mixed Lennard-Jones clusters: Global reparametrization and optimization**, Johannes M. Dieterich and Bernd Hartke [Christian-Albrechts-Universität]

As extended benchmarks to global cluster structure optimization methods, we provide a first systematic point of entry into the world of strongly mixed rare gas clusters. A new set of generalized Lennard-Jones pair potentials is generated for this purpose, by fitting them to high-end ab initio reference data.

- 1386–1399 **Consideration of data load time on modern processors for the Verlet table and linked-cell algorithms**, Eduard S. Fomin [Institute of Cytology and Genetics, SB RAS]

Neighbor search algorithms are widely used in molecular dynamics for the direct computation of short-range pairwise interatomic potentials. It is widely believed that the VT is more efficient than the LC. The analysis of these methods shows that in case when the average number of interactions per particle is relatively large, or more specifically, the particle density ρ and skin radius r_{skin} meet the condition $(4\pi/6) \rho r_{\text{skin}}^3/27 \gg 1$, which may be true for most simulations of liquids, the number of memory data load operations in the LC is much less than that in the VT.

- 1400–1410 **Combination of the CHARMM27 force field with united-atom lipid force fields**, Nicolas Sapay and D. Peter Tieleman [University of Calgary]

See Methodology / Potentials and Parameters.

- 1411–1423 **Bringing about matrix sparsity in linear-scaling electronic structure calculations**, Emanuel H. Rubensson [Uppsala University] and Elias Rudberg

The performance of linear-scaling electronic structure calculations depends critically on matrix sparsity. This article gives an overview of different strategies for removal of small matrix elements, with emphasis on schemes that allow for rigorous control of errors.

- 1424–1430 **Sensitivity analysis and uncertainty calculation for dispersion corrected density functional theory**, Felix Hanke [University of Liverpool]

The precision of binding energies and distances computed with dispersion-corrected density functional theory (DFT-D) is investigated by propagation of uncertainties, yielding relative uncertainties of several percent. Sensitivity analysis is used to calculate the geometry-dependent relative importance of each input parameter for the dispersion correction.

- 1431–1440 **Analyzing the robustness of the MM/PBSA free energy calculation method: Application to DNA conformational transitions**, Allyn R. Brice and Brian N. Dominy [Clemson University]

See Applications / Free energy computation.

- 1441–1448 **Cyclooctatetraene dianion—an artifact?**, Justyna Dominikowska and Marcin Palusiak [University of Łódź]

Cyclooctatetraene in its dianionic form (COT^{2-}) is considered to be partially or fully aromatic due to the fact that, unlike its neutral counterpart, it adopts planar structure with CC bonds equalized. However, some authors report that this dianion is neither planar nor aromatic. Thus, we performed a detailed analysis of the COT^{2-} case.

- 1449–1455 **Theoretical mechanistic study on the reaction of CN radical with HNCN**, Nan-Nan Wu, Chao-Zheng He, Xue-Mei Duan and Jing-Yao Liu [Jilin University]

The mechanism for the reaction of the cyanogen radical (CN) with the cyanomidyl radical (HNCN) has been investigated theoretically.

- 1456–1465 **Effect of the damping function in dispersion corrected density functional theory**, Stefan Grimme [Organisch-Chemisches Institut der Universität Münster], Stephan Ehrlich and Lars Goerigk

It is shown by an extensive benchmark on molecular energy data that the mathematical form of the damping function in DFT-D methods has only a minor impact on the quality of the results. For 12 different functionals, a standard “zero-damping” formula and rational damping to finite values for small interatomic distances according to Becke and Johnson (BJ-damping) has been tested.

Journal Of Molecular Modeling, 17(4), April, 2011.

- 621-631 **In Silico sequence analysis and molecular modeling of the three-dimensional structure of DAHP synthase from *Pseudomonas fragi***, Satya Tapas, Girijesh Kumar Patel, Sonali Dhindwal and Shailly Tomar [Indian Institute of Technology, Roorkee]

See Applications / Homology Modeling.

- 633-647 **Theoretical and experimental studies on the inhibition potentials of aromatic oxaldehydes for the corrosion of mild steel in 0.1 M HCl**, Nnabuk Okon Eddy [Ahmadu Bello University] and Benedict I. Ita

Experimental aspect of the inhibition of the corrosion of mild steel by oxaldehydes was carried out using gravimetric, gasometric and thermometric methods while the theoretical studies were carried out using quantum chemical principle and quantitative structure activity relation (QSAR) approaches.

- 649-655 **First principle study of cysteine molecule on intrinsic and Au-doped graphene surface as a chemosensor device**, Zhuxia Zhang, Husheng Jia, Fei Ma, Peide Han and Xuguang Liu, Bingshe Xu [Taiyuan University of Technology]

To search for a high sensitivity sensor for cysteine, we investigated the adsorption of cysteine on intrinsic and Au-doped graphene sheets using density functional theory calculations.

- 657-667 **Computer-aided molecular design of 1H-imidazole-2,4-diamine derivatives as potential inhibitors of Plasmodium falciparum DHFR enzyme**, Legesse Adane and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research (NIPER)]

See Applications / Medicinal Chemistry and Drug Design.

- 669-680 **Theoretical investigation of reactivities of amines in the N-nitrosation reactions by N₂O₃**, Zhi Sun, Yong Dong Liu [Beijing University of Technology] and Rugang Zhong

N-nitrosamine is a class of carcinogenic, mutagenic, and teratogenic compounds, which can be produced from N-nitrosation of amine by nitrosating agents. N-nitrosation of 19 amines (eight acyclic amines, five heterocyclic amines, and six amines with unsaturated groups) by N₂O₃ was investigated at the CBS -QB3 level of theory.

- 681-693 **Isolation, biological evaluation and 3D-QSAR studies of insecticidal/narcotic sesquiterpene polyol esters**, Shao-peng Wei, Zhi-qin Ji, Hui-xiao Zhang, Ji-wen Zhang and Yong-hua Wang [Northwest Agricultural & Forestry University], et al.

See Applications / QSAR.

- 695-699 **Covalent hybridization of CNT by thymine and uracil: A computational study**, Mahmoud Mirzaei, Hamid R. Kalhor and Nasser L. Hadipour [Tarbiat Modares University]

See Applications / Carbon Nanotubes.

- 701-708 **Computational characterization of sodium selenite using density functional theory**, Diana Barraza-Jiménez [A.C. Unidad Delicias], Manuel Alberto Flores-Hidalgo, Donald H. Galvan, Esteban Sánchez and Daniel Glossman-Mitnik

In this theoretical study we used density functional theory to calculate the molecular and crystalline structures of sodium selenite.

- 709-719 **Dielectric and conformational studies of 1-propanol and 1-butanol in methanol**, Baliram Lone [Dr. Babasaheb Ambedkar Marathwada University] and Vinjanampaty Madhurima

Hydrogen bonds in small chain alcohol-alcohol binary systems alter the dielectric permittivity of the binary system. With a view to obtain a better understanding of the interactions in such systems, the complex permittivity spectra of mixtures of methanol (ME) with 1-propanol (1PR) and 1-butanol (1BU) have been measured in the frequency range 10 MHz to 20 GHz using time domain reflectometry at 288 K, 298 K, 308 K and 318 K.

- 721-726 **Self-assembled monolayers of oligosilane on the silicon (001) surface: molecular dynamics simulations**, Li Zhao, Xue-Mei Duan, Xiang-Gui Xue, Ming-Hui Li and Ze-Sheng Li [Jilin University]

Surfaces, Catalysts and Materials

- 727-737 **Dynamical insight into Caenorhabditis elegans eIF4E recognition specificity for mono- and trimethylated structures of mRNA 5' cap**, Katarzyna Ruszczyńska-Bartnik, Maciej Maciejczyk and Ryszard Stolarski [University of Warsaw]

See Applications / Nucleic acids.

- 739-755 **Molecular dynamics simulations of Nafion and sulfonated polyether sulfone membranes. I. Effect of hydration on aqueous phase structure**, Takahiro Ohkubo [National Institute of Advanced Industrial Science and Technology (AIST)], Koh Kidena, Naohiko Takimoto and Akihiro Ohira

Surfaces, Catalysts and Materials

- 757-767 **Insight into the lithium/hydrogen bonding in $(\text{CH}_2)_2\text{X} \cdots \text{LiY}/\text{HY}$ (X: C=CH₂, O, S; Y=F, Cl, Br) complexes**, Xiaoyan Li, Yanli Zeng, XueYing Zhang, Shijun Zheng and Lingpeng Meng [Hebei Normal University]

The nature of the lithium/hydrogen bonding between $(\text{CH}_2)_2\text{X}$ (X: C=CH₂, O, S) and LiY/HY (Y=F, Cl, Br) have been theoretically investigated at MP2/6-311++G (d, p) level, using Bader's "atoms in molecules (AIM)" theory and Weinhold's "natural bond orbital (NBO)" methodology.

- 769-775 **Molecular dynamics investigation of psalmopeotoxin I. Probing the relationship between 3D structure, anti-malarial activity and thermal stability**, Matthew Paul Gleeson [Kasetsart University], Songpon Deechongkit and Somsak Ruchirawat

See Applications / Medicinal Chemistry and Drug Design.

- 777-784 **Potential use of some metal clusters as hydrogen storage materials—a conceptual DFT approach**, Santanab Giri, Arindam Chakraborty and Pratim Kumar Chattaraj [Indian Institute of Technology, Kharagpur]

Structure, stability and reactivity of several metal clusters with or without hydrogen doping were studied using standard ab initio and density functional theory (DFT) calculations.

- 785-794 **Predicting helium and neon adsorption and separation on carbon nanotubes by Monte Carlo simulation**, Zabiollah Bolboli Nojini [Shahid Chamran University], Amir Abbas Rafati, Seyed Majid Hashemianzadeh and Sepideh Samiee

See Applications / Carbon Nanotubes.

- 795-803 **Studying the mechanism that enables paullones to selectively inhibit glycogen synthase kinase 3 rather than cyclin-dependent kinase 5 by molecular dynamics simulations and free-energy calculations**, Quan Chen, Wei Cui, Yuanhua Cheng, Fushi Zhang and Mingjuan Ji [Graduate University of Chinese Academy of Sciences]

See Applications / Medicinal Chemistry and Drug Design.

- 805-810 **Triplet fluoranthenes: Aromaticity versus unpaired electrons**, Svetlana Marković [University of Kragujevac], Jelena Đurđević, Svetlana Jeremić and Ivan Gutman

Three fluoranthenes and one substituted fluoranthene, 2,2-dimethyl-2H-dibenzo[cd,k]fluoranthene, were investigated using the unrestricted symmetry-broken and complete active space methods.

- 811-816 **Molecular simulations of intermediate and long alkanes adsorbed on graphite: Tuning of non-bond interactions**, Lucyna Firlej, Bogdan Kuchta, Michael W. Roth [University of Northern Iowa] and Carlos Wexler

The interplay between the torsional potential energy and the scaling of the 1-4 van der Waals and Coulomb interactions determines the stiffness of flexible molecules. In this paper we demonstrate for the first time that the precise value of the nonbond scaling factor (SF)—often a value assumed without justification—has a significant effect on the critical properties and mechanisms of systems undergoing a phase transition, and that, for accurate simulations, this scaling factor is highly dependent on the system under consideration.

- 817-831 **Design of 1-arylsulfamido-2-alkylpiperazine derivatives as secreted PLA2 inhibitors**, Preethi Badrinarayan, P. Srivani and G. Narahari Sastry [Indian Institute of Chemical Technology, Tarnaka]

See Methodology / Ligand Docking.

- 833-849 **Computational design of a lipase for catalysis of the Diels-Alder reaction**, Mats Linder [Royal Institute of Technology (KTH)], Anders Hermansson, John Liebeschuetz and Tore Brinck

See Applications / Enzyme Catalysis.

- 851-856 **Evaluation of two-center Coulomb and hybrid integrals over complete orthonormal sets of α -ETO using auxiliary functions**, Israfil I. Guseinov and Ercan Sahin [Onsekiz Mart University]

By the use of ellipsoidal coordinates, the two-center Coulomb and hybrid integrals over complete orthonormal sets of Ψ_n -exponential type orbitals arising in ab initio calculations of molecules are evaluated, where $\alpha = 1, 0, -1, -2, \dots$.

- 857-868 **Instability of 2,2-di(pyridin-2-yl)acetic acid. Tautomerization versus decarboxylation**, Piotr Borowski [Maria Curie-Skłodowska University], Ryszard Gawinecki, Anna Miłaczewska, Agnieszka Skotnicka and Krzysztof Woliński, et al.

The DFT calculations at the B3LYP level with 6-311G** basis set were carried out in order to reveal whether tautomerization or decarboxylation is responsible for the instability of 2,2-di(pyridin-2-yl)acetic (DPA) and 1,8-diazafluorene-9-carboxylic (DAF) acids.

- 869-877 **Relationship between mutation of serine residue at 315th position in M. tuberculosis catalase-peroxidase enzyme and Isoniazid susceptibility: An in silico analysis**, Rituraj Purohit, Vidya Rajendran and Rao Sethumadhavan [Vellore Institute of Technology University]

See Applications / Medicinal Chemistry and Drug Design.

- 879-888 **Theoretical study on the aromaticity from d-AOs in cationic X_3^+ ($X = \text{Sc, Y, La}$) clusters**, Xian Xing Chi [WenZhou University] and Xing Zhan Lin

The stable structures and aromatic characters for three cationic X_3^+ ($X = \text{Sc, Y, and La}$) and three relevant neutral $X_3\text{Cl}$ ($X = \text{Sc, Y, La}$) clusters are investigated at the DFT and post HF level of theory.

- 889-898 **Solvation free energies of glutamate and its metal complexes: A computer simulation study**, Sepideh Ketabi [Islamic Azad University], Haleh Hashemi Haeri and Seyed Majid Hashemianzadeh

See Applications / Free energy computation.

- 899-911 **Allosteric transition and binding of small molecule effectors causes curvature change in central β -sheets of selected enzymes**, Ellen Tolonen, Brenda Bueno, Sanjeev Kulshreshta, Piotr Cieplak and Miguel Arg  ez, Boguslaw Stec [Sanford-Burnham Medical Research Institute], et al.

See Applications / Enzyme Catalysis.

- 913-920 **Theoretical study on interactions of β -cyclodextrin with helicobacter pylori eradicating agent (TG44)**, Xin Jin, Xueye Wang [Xiangtan University], Cuihuan Ren, Yuan Miao and Ling Yi

The inclusion complex of β -cyclodextrin (β -CD) and 4-methylbenzyl-4'-[trans-4-(guanidinomethyl)cyclohexylcarbonyloxy]-biphenyl-4-carboxylate monohydrochloride (TG44) had been investigated by using density functional theory (DFT) and PM3 semiempirical method.

Molecular Simulation, 37(5), 2011.

- 350 – 360 **Vapour-liquid phase equilibria of simple fluids confined in patterned slit pores**, Sudhir K. Singh [Indian Institute of Technology, Kanpur; Sandip Khan; Subimal Jana; Jayant K. Singh

We present the influence of surface heterogeneity on the vapour-liquid phase behaviour of square-well fluids in slit pores using grand-canonical transition-matrix Monte Carlo simulations along with the histogram-reweighting method.

- 361 – 368 **Novel hemagglutinin inhibitors for H1N1 influenza virus screening from TCM database**, Tung-Ti Chang [China Medical University]; Mao-Feng Sun; Hsin-Yi Chen; Fuu-Jen Tsai; Mark Fisher; Jaung-Geng Lin; Calvin Yu-Chian Chen

The emergence of Tamiflu (oseltamivir)-resistant viral strains in pandemic of H1N1/09 influenza virus has raised global awareness of anti-viral drug resistant issue. The purpose of this research is to design novel haemagglutinin (HA) inhibitor for inhibiting viral entry into the host cell. We performed structure-based drug design to analyse interactions between the potent inhibitor and HA.

- 369 – 378 **Theoretical study on the gas and solution phase enthalpies, free energies and equilibrium constants for the isomerisation of [1.1]paracyclophane derivatives as potential molecular switches**, Sierra Rayne [Ecologica Research, British Columbia]; Kaya Forest

Theoretical studies were conducted on the predicted gas and solution phase thermodynamic properties for isomerisation of various [1.1]paracyclophane derivatives to their corresponding transannular[4+4] adducts at representative levels of density functional and composite method theories.

- 379 – 385 **Alanine-based peptides containing polar residues presumably favour α -helical structure entropically**, Wankee Kim [Tokyo University of Science]; Ichiro Yamato; Tadashi Ando

See Applications / Protein Secondary Structure.

- 386 – 393 **Influence of HOCl...O₃ and HOCl...HOCl interactions on the stability of O₃(HOCl)₂ complexes: a theoretical study**, Hossein Roohi [University of Guilan]; Ali-Reza Nowroozi; Ali Ebrahimi; Fazlola Eshghi; Elham Ahmadi

We have analysed the role of HOCl...O₃ and HOCl...HOCl interactions on the stability of four estimated O₃(HOCl)₂ complexes by means of ab initio molecular orbital calculations.

- 394 – 413 **QSPR of antioxidant phenolic compounds using quantum chemical descriptors**, Indrani Mitra [Jadavpur University]; Achintya Saha; Kunal Roy

Accelerated systemic free radical production poses a serious problem to healthy living. Since long, phenolic antioxidants have been studied for their ability to react with these toxic radicals. The present work deals with a series of substituted phenolic derivatives with a wide range of antioxidant property data.

- 414 – 420 **Effect of the metal ion and the medium on the electronic structure of anthranilic acid: a modelling study on the Li and the BeH derivatives**, Tareq Irshaidat [Al-Hussein Bin Talal University]

This computational organic chemistry study illustrates that the size of the metal ion is a critical point in determining the bonding mode of the anthranilate (2-aminobenzoate).

- 421 – 429 **A molecular dynamics study to investigate the local atomic arrangements during martensitic phase transformations**, F. A. Celik [Bitlis Eren University]; A. K. Yildiz; S. Ozgen

In this study, the local atomic rearrangements caused by thermally induced martensitic phase transitions in Ni-37.5 at.%Al alloy model based on embedded atom method are studied using molecular dynamics simulations.

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1 APPLICATIONS (74)

Page 2

1.1 Small Molecules (15)

Water and Solvation	Page 2	QSAR	Page 5
Med. Chem. And Drug Design	Page 3	Carbon Nanoparticles	Page 5

1.2 Biopolymers (59)

Bioinformatics and Cheminformatics	Page 6	Enzyme Catalysis	Page 13
Protein Secondary Structure	Page 7	Protein-Protein Interactions	Page 16
Protein Structure Prediction	Page 7	Membrane Proteins	Page 16
Comparative or Homology Modeling	Page 8	Protein Folding	Page 18
Protein Dynamics	Page 8	Protein-Nucleic Acids	Page 19
Free Energy Calculations	Page 11	Nucleic Acids	Page 20
Ligand Binding	Page 12		

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (17)

Page 22

Potentials and Parameters	Page 22	Comparative or Homology	Page 24
Molecular Dynamics	Page 23	Ligand Docking	Page 25
QM & QM/MM	Page 23		

3 JOURNAL REVIEWS (4)

Page 27

Journal of Molecular Graphics and Modeling, 29 (7), June, 2011.
 Journal of Computational Chemistry, 32 (8), June, 2011.
 Journal of Computational Chemistry, 32 (9), July, 2011.
 Journal of Molecular Modeling, 17 (5), May, 2011.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 42

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Hydration Properties of α -, β -, and γ -Cyclodextrins from Molecular Dynamics Simulations

Madhurima Jana and Sanjoy Bandyopadhyay [Indian Institute of Technology, Kharagpur]

J. Phys. Chem. B., **115**, 6347–6357, 2011.

Atomistic molecular dynamics (MD) simulations of α -, β -, and γ -cyclodextrins (ACD, BCD, and GCD) in aqueous solutions have been performed. Detailed analyses were carried out to compare the microscopic properties of water confined within the cavities of these macromolecules and in the hydration layers around them. It is noticed that reduced tetrahedral ordering of water in and around the CD molecules are associated with their restricted motions. Interestingly, unlike the translational motions, the rotational motions of cavity water molecules are found to be highly dependent on cavity dimensions.

Role of bridging water molecules in GSK3 β -inhibitor complexes: Insights from QM/MM, MD, and molecular docking studies

Shao-Yong Lu, Yong-Jun Jiang [Zhejiang University], Jing Lv, Jian-Wei Zou and Tian-Xing Wu

J. Comp. Chem. **32**, 1907–1918, 2011.

The role of water molecules is increasingly gaining interest in drug design, and several studies have highlighted their paramount contributions to the specificity and the affinity of ligand binding. In this study, we employ the two-layer ONIOM-based quantum mechanics/molecular mechanics (QM/MM) calculations, molecular dynamics (MD) simulations, and molecular docking studies to investigate the effect of bridging water molecules at the GSK3 β -inhibitors interfaces.



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Medicinal Chemistry and Drug Design

Docking and quantitative structure–activity relationship studies for 3-fluoro-4-(pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)aniline, 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)aniline, and 4-(4-amino-2-fluorophenoxy)-2-pyridinylamine derivatives as c-Met kinase inhibitors

Julio Caballero [Universidad de Talca], Miguel Quiliano, Jans H. Alzate-Morales, Mirko Zimic and Eric Deharo

J. Comp. Aided Mol. Des. **25**, 349-369, 2011.

We have performed docking of 3-fluoro-4-(pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)aniline (FPTA), 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)aniline (FPPA), and 4-(4-amino-2-fluorophenoxy)-2-pyridinylamine (AFPP) derivatives complexed with c-Met kinase to study the orientations and preferred active conformations of these inhibitors. The study was conducted on a selected set of 103 compounds with variations both in structure and activity. In addition, the predicted biological activities of the c-Met kinase inhibitors, measured as IC₅₀ values were obtained by using quantitative structure–activity relationship (QSAR) methods.

Molecular dynamics simulation of drug uptake by polymer

M. Subashini, Padma V. Devarajan, Ganeshchandra S. Sonavane and Mukesh Doble [IIT-Madras]

J. Mol.Mod., **17**, 1141-1147, 2011.

Drug uptake by polymer was modeled using a molecular dynamics (MD) simulation technique. Three drugs—doxorubicin (water soluble), silymarin (sparingly water soluble) and gliclazide (water insoluble)—and six polymers with varied functional groups—alginic acid, sodium alginate, chitosan, Gantrez AN119 (methyl-vinyl–ether-co-malic acid based), Eudragit L100 and Eudragit RSPO (both acrylic acid based)—were selected for the study. The structures were modeled and minimized using molecular mechanics force field (MM+).

3D-QSAR and molecular docking studies of azaindole derivatives as Aurora B kinase inhibitors

Ping Lan, Wan-Na Chen, Ping-Hua Sun and Wei-Min Chen [Jinan University]

J. Mol.Mod., **17**, 1191-1205, 2011.

The Aurora kinases have been regarded as attractive targets for the development of new anticancer agents. Recently a series of azaindole derivatives with Aurora B inhibitory activities were reported. To explore the relationship between the structures of substituted azaindole derivatives and their inhibition of Aurora B, 3D-QSAR and molecular docking studies were performed on a dataset of 41 compounds. 3D-QSAR, including CoMFA and CoMSIA, were applied to identify the key structures impacting their inhibitory potencies.

Novel ligands that target the mitochondrial membrane protein mitoNEET

Robert M. Bieganski, Martin L. Yarmush [Harvard Medical School]

J. Mol.Graph. and Mod., **29**, 965-973, 2011.

Ligands of the thiazolidinedione (TZD) class of compounds, pioglitazone (Actos™) and rosiglitazone (Avandia™) are currently approved for treatment of type 2 diabetes and are known to bind to the PPAR-γ nuclear receptor subtype. In this study, a molecular blind docking (BD) method was used to discover potential mitoNEET LBS and novel ligands, utilizing the program AutoDock Vina (v 1.0.2).

Medicinal Chemistry and Drug Design (Cont'd)

Vibrational spectral signatures of peptide secondary structures: N-methylation and side chain hydrogen bond in cyclosporin A

Zheng-Wang Qu [Humboldt Universität zu Berlin], Hui Zhu and Volkhard May

J. Comp. Chem. **32**, 1500–1518, 2011.

Molecular dynamics simulations are performed to explore important conformations of cyclosporin A, an immunosuppressive cyclic undecapeptide drug, in different media including gas-phase, chloroform, and acetonitrile. Density functional theory calculations are used to refine the low-lying conformers and to predict their infrared and vibrational circular dichroism spectra. Vibrational spectral signatures in the important amide II, I, and A regions are identified for typical peptide secondary structures including β -turn (type II' or I), antiparallel β -sheet (flat or twisted), inverse γ -turn, N-methylated peptide bond, and side chain H-bond.

Pharmacophore alignment search tool: Influence of scoring systems on text-based similarity searching

Volker HÄhnke and Gisbert Schneider [Swiss Federal Institute of Technology (ETH) Zurich]

J. Comp. Chem. **32**, 1635–1647, 2011.

The text-based similarity searching method Pharmacophore Alignment Search Tool is grounded on pairwise comparisons of potential pharmacophoric points between a query and screening compounds. The underlying scoring matrix is of critical importance for successful virtual screening and hit retrieval from large compound libraries. Here, we compare three conceptually different computational methods for systematic deduction of scoring matrices: assignment-based, alignment-based, and stochastic optimization.

Identification of pentacyclic triterpenes derivatives as potent inhibitors against glycogen phosphorylase based on 3D-QSAR studies

Zhongjie Liang, Liying Zhang, Lianchun Li, Jun Liu, Hongling Li, Luyong Zhang, Limin Chen, Keguang Cheng, Mingyue Zheng, Xiaolan Wen, Pu Zhang, Jia Hao, Yanchun Gong, Xia Zhang, Xiaoyun Zhu, Jun Chen, Hong Liu, Hualiang Jiang, Cheng Luo, Hongbin Sun [China Pharmaceutical University]

Europ. Jou. Med. Chem., **46**, 1672–1681, 2011.

Naturally occurring pentacyclic triterpenes (PT), a novel class of inhibitors against glycogen phosphorylase (GP), hold promise for the treatment of type-2 diabetes and other diseases with disorders in glycogen metabolism. To identify novel and more potent GP inhibitors, the receptor-based comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA) approaches were performed to investigate the quantitative structure–activity relationships (QSAR) among 106 PT analogues.

Using the TOPS-MODE approach to fit multi-target QSAR models for tyrosine kinases inhibitors

Giovanni Marzaro [University of Santiago de Compostela], Adriana Chilin, Adriano Guiotto, Eugenio Uriarte, Paola Brun, Ignazio Castagliuolo, Francesca Tonus, Humberto González-Díaz

Europ. Jou. Med. Chem., **46**, 2185–2192, 2011.

Tyrosine kinases constitute an eligible class of target for novel drug discovery. They resulted often overexpressed and/or deregulated in several cancer diseases. Thus, the development of novel tyrosine kinases inhibitors is of value, as well as the finding of novel cheminformatic tools for their design. Among the different ways to rationally design novel compounds, the QSAR plays a key role. The QSAR approach, in fact, allow the prediction of activity against a number of targets (multi-target QSAR), thus leading to models able to predict not only the activity of a compound, but also its selectivity versus a set of targets.

Medicinal Chemistry and Drug Design (Cont'd)

Avoidance of the Ames test liability for aryl-amines via computation

Patrick McCarren, Gregory R. Bebernitz, Peter Gedeck, Susanne Glowienke, Melissa S. Grondine, Louise C. Kirman, Jacob Klickstein, Herbert F. Schuster, Lewis Whitehead [Novartis Institutes for Biomedical Research]

Bioorg. and Med.Chem., **19**, 3173-3182, 2011.

Aryl-amines are commonly used synthons in modern drug discovery, however a minority of these chemical templates have the potential to cause toxicity through mutagenicity. The toxicity mostly arises through a series of metabolic steps leading to a reactive electrophilic nitrenium cation intermediate that reacts with DNA nucleotides causing mutation. Highly detailed in silico calculations of the energetics of chemical reactions involved in the metabolic formation of nitrenium cations have been performed.

Quantitative Structure-Activity Relations

Molecular modeling and QSAR studies of a set of indole and benzimidazole derivatives as H₄ receptor antagonists

Joao Paulo S. Fernandes [Universidade de São Paulo], Kerly Fernanda M. Pasqualoto, Elizabeth I. Ferreira and Carlos A. Brandt

J. Mol.Mod., **17**, 921-928, 2011.

Histamine is an important biogenic amine, which acts with a group of four G-protein coupled receptors (GPCRs), namely H₁ to H₄ (H₁R – H₄R) receptors. The actions of histamine at H₄R are related to immunological and inflammatory processes, particularly in pathophysiology of asthma, and H₄R ligands having antagonistic properties could be helpful as antiinflammatory agents. In this work, molecular modeling and QSAR studies of a set of 30 compounds, indole and benzimidazole derivatives, as H₄R antagonists were performed.

Docking and 3D-QSAR modeling of cyclin-dependent kinase 5/p25 inhibitors

Zaheer Ul Haq [University of Karachi], Reaz Uddin, Lam Kok Wai, Abdul Wadood and Nordin Haji Lajis

J. Mol.Mod., **17**, 1149-1161, 2011.

Structure-based 3D-QSAR approaches (CoMFA and CoMSIA) were applied to understand the structural requirements of the Cyclin-dependent kinase 5/p25 inhibitors. Cyclin-dependent kinase 5 (CDK5) is believed to play an important role in the development of the central nervous system during the process of mammalian embryogenesis. Genetic algorithm based docking program (GOLD) was successfully utilized to orient the compounds inside the binding pocket of the CDK5/p25 structure. The adapted alignment method with the suitable parameters resulted in a reliable model.

Carbon Nanoparticles

Gating of a Water Nanochannel Driven by Dipolar Molecules

X. W. Meng, Y. Wang, Y. J. Zhao, and J. P. Huang [Fudan University]

J. Phys. Chem. B., **115**, 4768–4773, 2011.

On the basis of molecular dynamics simulations, we investigate water permeation across a single-walled carbon nanotube (SWCNT) under the influence of four symmetrical half-rings, each having six LiF dipolar molecules. The flux remains almost fixed as the separation, R, between the rings and SWCNT is larger than 1.562 nm, but decreases significantly as 0.944 nm < R < 1.562 nm, and reaches zero as R < 0.944 nm. This nanochannel shows an excellent on-off gate that is both effectively resistant to dipole noises and sensitive to available signals.

Carbon Nanoparticles (Cont'd)

Vibrational Energy Transfer between Carbon Nanotubes and Nonaqueous Solvents: A Molecular Dynamics Study

Tammie R. Nelson, Vitaly V. Chaban, Victor V. Prezhdo, and Oleg V. Prezhdo [University of Rochester]

J. Phys. Chem. B., **115**, 5260–5267, 2011.

We report molecular dynamics (MD) simulation of energy exchange between single-walled carbon nanotubes (CNTs) and two aprotic solvents, acetonitrile and cyclohexane. Following our earlier study of hydrated CNTs, we find that the time scales and molecular mechanisms of the energy transfer are largely independent of the nature of the surrounding medium, and therefore, should hold for other media including polymer matrices and DNA. The energy exchange time-scales are significantly influenced by the arrangement of solvent molecules inside CNTs.

1.2. <i>Biopolymers</i>

Bioinformatics and Cheminformatics

CycloPs: Generating Virtual Libraries of Cyclized and Constrained Peptides Including Nonnatural Amino Acids

Fergal J. Duffy [University College Dublin], Melanie Verniere, Marc Devocelle, Elise Bernard, Denis C. Shields, and Anthony J. Chubb

J.Chem. Infor. and Mod. **51**, 829–836, 2011.

We introduce CycloPs, software for the generation of virtual libraries of constrained peptides including natural and nonnatural commercially available amino acids. The software is written in the cross-platform Python programming language, and features include generating virtual libraries in one-dimensional SMILES and three-dimensional SDF formats, suitable for virtual screening. The stand-alone software is capable of filtering the virtual libraries using empirical measurements, including peptide synthesizability by standard peptide synthesis techniques, stability, and the druglike properties of the peptide.

Rationalizing the Role of SAR Tolerance for Ligand-Based Virtual Screening

Peter Ripphausen, Britta Nisius, Mathias Wawer, and Jorgen Bajorath [Rheinische Friedrich-Wilhelms-Universitat]

J.Chem. Infor. and Mod. **51**, 837–842, 2011.

It is well appreciated that the results of ligand-based virtual screening (LBVS) are much influenced by methodological details, given the generally strong compound class dependence of LBVS methods. It is less well understood to what extent structure–activity relationship (SAR) characteristics might influence the outcome of LBVS. We have assessed the hypothesis that the success of prospective LBVS depends on the SAR tolerance of screening targets, in addition to methodological aspects. In this context, SAR tolerance is rationalized as the ability of a target protein to specifically interact with series of structurally diverse active compounds.

Bioinformatics and Cheminformatics (Cont'd)

The MEMPACK alpha-helical transmembrane protein structure prediction server

Timothy Nugent, Sean Ward, and David T. Jones [University College London]

Bioinformatics. **27**, 1438-1439, 2011.

The experimental difficulties of alpha-helical transmembrane protein structure determination make this class of protein an important target for sequence-based structure prediction tools. The MEMPACK prediction server allows users to submit a transmembrane protein sequence and returns transmembrane topology, lipid exposure, residue contacts, helix-helix interactions and helical packing arrangement predictions in both plain text and graphical formats using a number of novel machine learning-based algorithms.

Protein Secondary Structure

Secondary Structure Assignment of Amyloid- β Peptide Using Chemical Shifts

Geoffrey P. F. Wood [BCH 4107 EPF Lausanne] and Ursula Rothlisberger

J. Chem. Theor. and Comp., **7**, 1552–1563, 2011.

The distinct conformational dependence of chemical shifts caused by α -helices and β -sheets renders NMR chemical shift analysis a powerful tool for the structural determination of proteins. However, the time scale of NMR experiments can make a secondary structure assignment of highly flexible peptides or proteins, which may be converting between conformational substates, problematic. In this paper, we explore the possible reasons for this discrepancy and show that the different results from experiments and theory are not necessarily mutually exclusive but may reflect a general problem of secondary structure assignment of conformationally flexible biomolecules.

Protein Structure Prediction

Protein structure prediction using a docking-based hierarchical folding scheme

Ilona Kifer, Ruth Nussinov and Haim J. Wolfson [Tel Aviv University]

Proteins: Stru. Fun. and Bioinfo. **79**, 1759–1773, 2011.

The pathways by which proteins fold into their specific native structure are still an unsolved mystery. This work is based on the premise that proteins fold in a hierarchical manner. We present FOBIA, an automated method for predicting a protein structure. FOBIA consists of two main stages: the first finds matches between parts of the target sequence and independently folding structural units using profile-profile comparison. The second assembles these units into a 3D structure by searching and ranking their possible orientations toward each other using a docking-based approach.

Comparative or Homology Modeling

Structural insights into transient receptor potential vanilloid type 1 (TRPV1) from homology modeling, flexible docking, and mutational studies

Jin Hee Lee, Yoonji Lee, HyungChul Ryu, Dong Wook Kang, Sun Choi [Ewha Womans University] and Jeewoo Lee, et al.

J. Comp. Aided Mol. Des. **25**, 317-327, 2011.

The transient receptor potential vanilloid subtype 1 (TRPV1) is a non-selective cation channel composed of four monomers with six transmembrane helices (TM1–TM6). TRPV1 is found in the central and peripheral nervous system, and it is an important therapeutic target for pain relief. We describe here the construction of a tetrameric homology model of rat TRPV1 (rTRPV1). We experimentally evaluated by mutational analysis the contribution of residues of rTRPV1 contributing to ligand binding by the prototypical TRPV1 agonists, capsaicin and resiniferatoxin (RTX).

Identification of hotspot regions of MurB oxidoreductase enzyme using homology modeling, molecular dynamics and molecular docking techniques

Vivek Kumar, Parameswaran Saravanan, Akanksha Arvind and C. Gopi Mohan [National Institute of Pharmaceutical Education and Research, Punjab]

J. Mol.Mod., **17**, 939-953, 2011.

Despite the availability of effective chemotherapy and a moderately protective vaccine, new anti-tuberculosis agents are urgently needed to decrease the global incidence of tuberculosis (TB) disease. The MurB gene belongs to the bacterial cell wall biosynthesis pathway and is an essential drug target in Mycobacterium tuberculosis (Mtb) that has no mammalian counterparts. Here, we present an integrated approach involving homology modeling, molecular dynamics and molecular docking studies on Mtb-MurB oxidoreductase enzyme.

Protein Dynamics

The CLN025 Decapeptide Retains a β -Hairpin Conformation in Urea and Guanidinium Chloride

Marcus P. D. Hatfield, Richard F. Murphy, and Sandor Lovas [Creighton University]

J. Phys. Chem. B., **115**, 4971–4981, 2011.

The conformational stability of the β -hairpin miniprotein, CLN025, a variant of chignolin in which the N- and C-terminal glycines are replaced by tyrosines, in various concentrations of guanidinium chloride (GdmCl) and urea was examined by molecular dynamics simulations and electronic circular dichroism (ECD) spectropolarimetry. The peptide maintains its β -hairpin conformation in GdmCl and urea solutions. In GdmCl, Gly7 influences the turn to reduce the number of Asp3–Gly7 H-bonds and the Tyr1–Trp9 H-bond is lost.

Molecular modeling and dynamics simulation of a histidine-tagged cytochrome b5

Ying-Wu Lin [University of South China], Tian-Lei Ying and Li-Fu Liao

J. Mol.Mod., **17**, 971-978, 2011.

Although an affinity tag such as six consecutive histidines, (His)₆-tag, has been widely used to obtain high quantity of recombinant proteins, little is known about its influences on heme proteins for lack of structural information. When (His)₆-tag was introduced to the N-terminus of a small heme protein, cytochrome b₅, experimental results showed the resultant protein, (His)₆-cyt b₅, has similar property and function to that of isolated cyt b₅. To provide structural information for this observation, we herein performed a structural prediction of (His)₆-cyt b₅ by molecular modeling in combination with molecular dynamics simulation.

Protein Dynamics (Cont'd)

Homology model and potential virus-capsid binding site of a putative HEV receptor Grp78

Hai Yu, Shaowei Li [Xiamen University], Chunyan Yang, Minxi Wei and Cuiling Song, et al.

J. Mol.Mod., **17**, 987-995, 2011.

P239, a truncated construct of the hepatitis E virus (HEV) ORF2 protein, has been proven able to bind with a chaperone, Grp78, in both an in vitro co-immune precipitation test and an in vivo cell model. We previously solved the crystal structure of E2s—the C-terminal domain of p239 involved in host interactions. In the present study, we built a 3D structure of Grp78 using homology modeling methods, and docked this molecule with E2s using the Zdockpro module of the InsightII software package.

ATP and its N6-substituted analogues: parameterization, molecular dynamics simulation and conformational analysis

Paweł Gruszczyński [University of Gdańsk], Krzysztof Smalara, Michał Obuchowski and Rajmund Kaźmierkiewicz

J. Mol.Mod., **17**, 1081-1090, 2011.

In this work we used a combination of classical molecular dynamics and simulated annealing techniques to shed more light on the conformational flexibility of 12 adenosine triphosphate (ATP) analogues in a water environment. We present simulations in AMBER force field for ATP and 12 published analogues [Shah et al. (1997) Proc Natl Acad Sci USA 94: 3565–3570]. The calculations were carried out using the generalized Born (GB) solvation model in the presence of the cation Mg^{2+} .

Molecular dynamics simulations of the minor ampullate spidroin modular amino acid sequence from *Parawixia bistriata*: insights into silk tertiary structure and fibre formation

André M. Murad and Elíbio L. Rech [Parque Estação Biológica – PqEB]

J. Mol.Mod., **17**, 1183-1189, 2011.

Spider fibres are primarily composed of proteins that are secreted by specialised glands found in different groups of arthropods. Herein, we present MD simulations of partial sequences from minor ampullate Spidroin (MiSp) silk of the Brazilian species *Parawixia bistriata*. Our data show that the formation of β -sheet structures is directly related to the N-terminal alignment of the modules. The N-terminal alignment gives rise to a high number of hydrogen bonds whose formation is driven by repeated alanine (Ala) sequences, which, in turn, lead to increased fibre strength.

dxTuber: Detecting protein cavities, tunnels and clefts based on protein and solvent dynamics

Martin Raunest, Christian Kandt [University of Bonn]

J. Mol.Graph. and Mod., **29**, 895-905, 2011.

Empty space in a protein structure can provide valuable insight into protein properties such as internal hydration, structure stabilization, substrate translocation, storage compartments or binding sites. This information can be visualized by means of cavity analysis. Here we report a novel, grid-based cavity detection method that uses protein and solvent residence probabilities derived from molecular dynamics simulations to identify (I) internal cavities, (II) tunnels or (III) clefts on the protein surface.

Protein Dynamics (Cont'd)

Binding modes of diketo-acid inhibitors of HIV-1 integrase: A comparative molecular dynamics simulation study

Meilan Huang [Queens University Belfast], Guy H. Grant, W. Graham Richards

J. Mol. Graph. and Mod., **29**, 956-964, 2011.

HIV-1 integrase (IN) has become an attractive target since drug resistance against HIV-1 reverse transcriptase (RT) and protease (PR) has appeared. Diketo acid (DKA) inhibitors are potent and selective inhibitors of HIV-1 IN: however the action mechanism is not well understood. Here, to study the inhibition mechanism of DKAs we performed 10 ns comparative molecular dynamics simulations on HIV-1 IN bound with three most representative DKA inhibitors: Shionogi inhibitor, S-1360 and two Merck inhibitors L-731,988 and L-708,906.

Molecular Dynamics Studies on the Structural Stability of Wild-type Dog Prion Protein

Jiapu Zhang [University of Ballarat], David D.W. Liu

J. Biomol. Stru. and Dyn., **28**, 845-860, 2011.

Prion diseases such as Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob diseases, Gerstmann-Sträussler-Scheinker syndrome, Fatal Familial Insomnia, Kuru in humans, scrapie in sheep, bovine spongiform encephalopathy (or 'mad-cow' disease) and chronic wasting disease in cattle are invariably fatal and highly infectious neurodegenerative diseases affecting humans and animals. This paper studies the molecular structural dynamics of wild-type dog prion protein. The comparison analyses with rabbit prion protein show that the dog prion protein has stable molecular structures whether under neutral or low pH environments.

Structural and Thermodynamic Investigations on the Aggregation and Folding of Acylphosphatase by Molecular Dynamics Simulations and Solvation Free Energy Analysis

Song-Ho Chong, Chewook Lee, Guipeun Kang, Mirae Park, and Sihyun Ham [Sookmyung Women's University]

J. Am. Chem. Soc., **133**, 7075-7083, 2011.

Protein engineering method to study the mutation effects on muscle acylphosphatase (AcP) has been actively applied to describe kinetics and thermodynamics associated with AcP aggregation as well as folding processes. To this end, we have investigated the mutation effects on the structures and thermodynamics for the aggregation and folding of AcP by using the combination of fully atomistic, explicit-water molecular dynamics simulations, and three-dimensional reference interaction site model theory. The results indicate that the A30G mutant with the fastest experimental aggregation rate displays considerably decreased α 1-helical contents as well as disrupted hydrophobic core compared to the wild-type AcP.

The Amyloid Formation Mechanism in Human IAPP: Dimers Have β -Strand Monomer-Monomer Interfaces

Nicholas F. Dupuis, Chun Wu, Joan-Emma Shea, and Michael T. Bowers [University of California Santa Barbara]

J. Am. Chem. Soc., **133**, 7240-7243, 2011.

Early oligomerization of human IAPP (hIAPP) is responsible for β -cell death in the pancreas and is increasingly considered a primary pathological process linked to Type II Diabetes (T2D). Here, we describe the first experimental data on the isolated and unmodified dimers of human (hIAPP) and nonamyloidogenic rat IAPP (rIAPP). The experiments reveal that the human IAPP dimers are more extended than those formed by rat IAPP and likely descend from extended monomers.

Protein Dynamics (Cont'd)

Molecular dynamics simulation of mammalian 15S-lipoxygenase with AMBER force field

Syed Tarique Moin, Thomas S. Hofer, Rabia Sattar and Zaheer Ul-Haq [University of Karachi]

Europ. Biophys. Jou., **40**, 715-726, 2011.

A molecular dynamics simulation study of mononuclear iron 15S-lipoxygenase (15S-LOX) from rabbit reticulocytes was performed to investigate its structure and dynamics; newly developed AMBER force field parameters were employed for the first coordination sphere of the catalytic iron (II). The results obtained from this study demonstrate that the structural features of the catalytic iron coordination site are in good agreement with available data obtained from experiments. The motional flexibility of the N-terminal β -barrel domain is greater than the C-terminal catalytic domain; flexibility was assessed in terms of B-factors and secondary structure calculations.

Systematic Examination of Polymorphism in Amyloid Fibrils by Molecular-Dynamics Simulation

Joshua T. Berryman, Sheena E. Radford, Sarah A. Harris [University of Leeds]

Biophysical Journal. **100**, 2234-2242, 2011.

Amyloid fibrils often exhibit polymorphism. Polymorphs are formed when proteins or peptides with identical sequences self-assemble into fibrils containing substantially different arrangements of the β -strands. We used atomistic molecular-dynamics simulation to examine the thermodynamic stability of a amyloid fibrils in different polymorphic forms by performing a systematic investigation of sequence and symmetry space for a series of peptides with a range of physicochemical properties.

Free Energy Calculations

A Simple QM/MM Approach for Capturing Polarization Effects in Protein-Ligand Binding Free Energy Calculations

Frank R. Beierlein, Julien Michel, and Jonathan W. Essex [University of Southampton]

J. Phys. Chem. B., **115**, 4911–4926, 2011.

We present a molecular simulation protocol to compute free energies of binding, which combines a QM/MM correction term with rigorous classical free energy techniques, thereby accounting for electronic polarization effects. Relative free energies of binding are first computed using classical force fields, Monte Carlo sampling, and replica exchange thermodynamic integration. Snapshots of the configurations at the end points of the perturbation are then subjected to DFT-QM/MM single-point calculations using the B3LYP functional and a range of basis sets.

Predicting Fixation Tendencies of the H3N2 Influenza Virus by Free Energy Calculation

Keyao Pan and Michael W. Deem [Rice University]

J. Chem. Theor. and Comp., **7**, 1259–1272, 2011.

The influenza virus evolves to escape from immune system antibodies that bind to it. We used free energy calculations with Einstein crystals as reference states to calculate the difference of antibody binding free energy ($\Delta\Delta G$) induced by amino acid substitution at each position in epitope B of the H3N2 influenza hemagglutinin, the key target for antibodies. A substitution with a positive $\Delta\Delta G$ value decreases the antibody binding constant and increases viral fitness.

Free Energy Calculations (Cont'd)

Efficient Solvation Free Energy Calculations of Amino Acid Analogs by Expanded Ensemble Molecular Simulation

Andrew S. Paluch, Jindal K. Shah, and Edward J. Maginn [University of Notre Dame]

J. Chem. Theor. and Comp. **7**, 1394–1403, 2011.

We present an efficient, automated expanded ensemble method to calculate the residual chemical potential or solvation free energy by molecular dynamics simulation. The methodology is validated by computing the residual chemical potential of 13 amino acid analogs in water at 300 K and 1 bar and comparing to reference simulation data. Overall agreement is good, with the methodology of the present study reaching limiting precisions of less than 0.1 $k_B T$ in half of the total simulation time of the reference simulation study which utilized Bennett's acceptance ratio method.

Calculation of binding free energies of inhibitors to plasmepsin II

Denise Steiner, Chris Oostenbrink, François Diederich, Martina Zürcher and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich]

J. Comp. Chem. **32**, 1801–1812, 2011.

An understanding at the atomic level of the driving forces of inhibitor binding to the protein plasmepsin (PM) II would be of interest to the development of drugs against malaria. To this end, three state of the art computational techniques to compute relative free energies—thermodynamic integration (TI), Hamiltonian replica-exchange (H-RE) TI, and comparison of bound versus unbound ligand energy and entropy—were applied to a protein-ligand system of PM II and several exo-3-amino-7-azabicyclo[2.2.1]heptanes and the resulting relative free energies were compared with values derived from experimental IC_{50} values.

Ligand Binding/Docking

Ligand Conformational and Solvation/Desolvation Free Energy in Protein–Ligand Complex Formation

Michal Kolar, Jindrich Fanfrlik, and Pavel Hobza [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B. **115**, 3146–3154, 2011.

In this study, an extensive sampling of the conformational space of nine HIV-1 protease inhibitors was performed to estimate the uncertainty with which a single-conformation scoring scheme approximates the ligand–protein binding free energy. The SMD implicit solvation/desolvation energy and gas-phase PM6-DH2 energy were calculated for a set of 1600 conformations of each ligand. The probability density functions of the energies were compared with the values obtained from the single-conformation approach and from a short ab initio molecular dynamics simulation.

Binding Affinities of Factor Xa Inhibitors Estimated by Thermodynamic Integration and MM/GBSA

Samuel Genheden, Ingemar Nilsson, and Ulf Ryde [Lund University]

J. Chem. Infor. and Mod. **51**, 829–836, 2011.

We present free energy estimates of nine 3-amidinobenzyl-1H-indole-2-carboxamide inhibitors of factor Xa. Using alchemical thermodynamic integration (TI) calculations, we estimate the difference in binding free energies with high accuracy and precision, except for mutations involving one of the amidinobenzyl rings. Crystal studies show that the inhibitors may bind in two distinct conformations, and using TI, we show that the two conformations give a similar binding affinity.

Ligand Binding / Docking (Cont'd)

Study of interactions between Mycobacterium tuberculosis proteins: SigK and anti-SigK

Vasavi Malkhed [Nizam College, Osmania University],
Bargavi Gudlur, Bhargavi Kondagari, Ramasree Dulapalli and
Uma Vuruputuri

J. Mol.Mod., **17**, 1109-1119, 2011.

The development of novel antituberculosis therapeutic molecules is a global health concern. Complex gene expression in Mycobacterium tuberculosis is mediated mainly by various sigma factors. The SigK protein binds to RNA polymerase, facilitating the expression of genes encoding the antigenic proteins mpt70 and mpt83. This study focuses on the interactions between SigK and the N-terminal domain of anti-SigK. The 3D structures of SigK (187 residues) and the N-terminal domain of anti-SigK (92 residues) are elucidated, using the crystal structures of the A and B chains of sigma E and anti-sigma ChrR of Rhodobacter spheroides (PDB code: 2Q1Z) as templates, respectively.

Molecular modelling and competition binding study of Br-noscapine and colchicine provide insight into noscapinoid-tubulin binding site

Pradeep K. Naik, Seneha Santoshi, Ankit Rai, Harish C. Joshi
[Emory University School of Medicine]

J. Mol.Graph. and Mod., **29**, 947-955, 2011.

We have previously discovered the tubulin-binding anti-cancer properties of noscapine and its derivatives (noscapinoids). Here, we present three lines of evidence that noscapinoids bind at or near the well studied colchicine binding site of tubulin. The simplest interpretation of these collective data is that Br-noscapine binds tubulin at a site overlapping with, or very close to colchicine-binding site of tubulin. Although we cannot rule out a formal possibility that Br-noscapine might bind to a site distinct and distant from the colchicine-binding site that might negatively influence the colchicine binding to tubulin.

Enzyme Catalysis

A comparison of the dynamics of pantothenate synthetase from M. tuberculosis and E. coli: Computational studies

Yaw Sing Tan, Gloria Fuentes and Chandra Verma
[Bioinformatics Institute (A*STAR)]

Proteins: Stru. Fun. and Bioinfo. **79**, 1715–1727, 2011.

Pantothenate synthetase (PS) catalyzes the final step of the pantothenate pathway, in which pantothenate is formed from pantoate and β -alanine in an ATP-dependent reaction. Mycobacterium tuberculosis PS (MTB PS) is functionally a dimer and a potential target for novel antitubercular drugs. Molecular dynamics simulations show that the functional dynamics of the enzyme are dominated by motions of a flexible gate loop in the N-terminal domain and of the C-terminal domain.

Dynamic flaps in HIV-1 protease adopt unique ordering at different stages in the catalytic cycle

Suresh Karthik and Sanjib Senapati [Indian Institute of
Technology Madras]

Proteins: Stru. Fun. and Bioinfo. **79**, 1830–1840, 2011.

The flexibility of HIV-1 protease flaps is known to be essential for the enzymatic activity. Here we attempt to capture a multitude of conformations of the free and substrate-bound HIV-1 protease that differ drastically in their flap arrangements. The substrate binding process suggests the opening of active site gate in conjunction with a reversal of flap tip ordering, from the native semiopen state. The reversed-flap, open-gated enzyme readily transforms to a closed conformation after proper placement of the substrate into the binding cleft.

Enzyme Catalysis (Cont'd)

Molecular dynamics and docking simulations as a proof of high flexibility in *E. coli* FabH and its relevance for accurate inhibitor modeling

Yunierkis Pérez-Castillo [Katholieke Universiteit Leuven],
Matheus Froeyen, Miguel Ángel Cabrera-Pérez and Ann
Nowé

J. Comp. Aided Mol. Des. **25**, 371-393, 2011.

Bacterial β -ketoacyl-acyl carrier protein synthase III (FabH) has become an attractive target for the development of new antibacterial agents which can overcome the increased resistance of these pathogens to antibiotics in clinical use. Despite several efforts have been dedicated to find inhibitors for this enzyme, it is not a straightforward task, mainly due its high flexibility which makes difficult the structure-based design of FabH inhibitors. Here, we present for the first time a Molecular Dynamics (MD) study of the *E. coli* FabH enzyme to explore its conformational space.

Computational Mechanistic Studies Addressed to the Transamination Reaction Present in All Pyridoxal 5'-Phosphate-Requiring Enzymes

N. M. F. S. A. Cerqueira, P. A. Fernandes, and M. J. Ramos
[Universidade do Porto]

J. Chem. Theor. and Comp. **7**, 1356–1368, 2011.

The pyridoxal-5'-phosphate-dependent enzymes (PLP enzymes) catalyze a myriad of biochemical reactions, being actively involved in the biosynthesis of amino acids and amino acid-derived metabolites as well as in the biosynthetic pathways of amino sugars and in the synthesis or catabolism of neurotransmitters. In this paper, density functional methods have been applied to investigate this common step present in all PLP-dependent enzymes—the transamination reaction.

Quantum Chemical Modeling of Enzymatic Reactions: The Case of Decarboxylation

Rong-Zhen Liao, Jian-Guo Yu, and Fahmi Himo [Stockholm
University]

J. Chem. Theor. and Comp. **7**, 1494–1501, 2011.

We present a systematic study of the decarboxylation step of the enzyme aspartate decarboxylase with the purpose of assessing the quantum chemical cluster approach for modeling this important class of decarboxylase enzymes. Active site models ranging in size from 27 to 220 atoms are designed, and the barrier and reaction energy of this step are evaluated. To model the enzyme surrounding, homogeneous polarizable medium techniques are used with several dielectric constants.

Computational study on the interaction of a ring-hydroxylating dioxygenase from *Sphingomonas* CHY-1 with PAHs

Vito Librando [Università di Catania], Matteo Pappalardo

J. Mol. Graph. and Mod. **29**, 915-919, 2011.

The massive computational resources available in the framework of a grid paradigm approach represent an emerging tool in the bioinformatics field. In this paper, we used the above approach in the rapid determination of the interactions between the ring-hydroxylating dioxygenase, comprised six enzymatic subunits, and polycyclic aromatic hydrocarbons (PAHs) in their optimal positions. The results were obtained by simulating enzyme dynamics at 300 K through molecular dynamics calculations.

Enzyme Catalysis (Cont'd)

Modeling of Transition State by Molecular Dynamics. Prediction of Catalytic Efficiency of the Mutants of Mandelate Racemase

Mei Zhuohang, Liu Ji, Yu Hongwei [Zhejiang University]

J. Biomol. Stru. and Dyn., **28**, 871-879, 2011.

Modeling of transition state by molecular dynamic method often requires modification of the force field parameters to describe energy profile accurately. In this work, we avoided the modification by modeling a series of mutants at binding-related site. In predicting the catalytic efficiency (k_{cat}/K_m) of the mutants of mandelate racemase (MR), the prediction performance of three energy subsets was investigated. It was indicated that the interaction-energy subset exhibited better prediction performance than whole-system subset and binding-site subset in both quantity and trend.

The Key Residues of Active Sites on the Catalytic Fragment for Paclitaxel Interacting with Poly (ADP-Ribose) Polymerase

Yue Wang, Fuyong Bian, Shengrong Deng, Qiang Shi, Maofa Ge, Shu Wang, Xingkang Zhang, Sichuan Xu [Yunnan University]

J. Biomol. Stru. and Dyn., **28**, 881-893, 2011.

Poly(ADP-ribose) polymerase (PARP) is regarded as a target protein for paclitaxel (PTX) to bind. An important issue is to identify the key residues as active sites for PTX interacting with PARP, which will help to understand the potential drug activity of PTX against cancer cells. Using docking method and MD simulation, we have constructed a refined structure of PTX docked on the catalytic function domain of PARP (PDB code: 1A26). The residues Glu327(988), Tyr246(907), Lys242(903), His165(826), Asp105(766), Gln102(763) and Gln98(759) in PARP are identified as potential sites involved in interaction with PTX according to binding energy (E_b) between PTX and single residue calculated with B3LYP/6-31G(d,p).

Molecular Modeling of Mycobacterium Tuberculosis dUTPase: Docking and Catalytic Mechanism Studies

Teodorico C. Ramalho [Federal University of Lavras], Melissa S. Caetano, Daniela Josa, Gustavo P. Luz, Elisangela A. Freitas, Elaine F. F. da Cunha

J. Biomol. Stru. and Dyn., **28**, 907-917, 2011.

Mycobacterium tuberculosis is a leading cause of infectious disease in the world today. Therefore, dUTPase was selected as a target enzyme to combat M. tuberculosis. In this work, molecular modeling methods involving docking and QM/MM calculations were carried out to investigate the binding orientation and predict binding affinities of some potential dUTPase inhibitors. Our results suggest that the best potential inhibitor investigated, among the compounds studied in this work, is the compound dUPNPP.

Zinc Chelation with Hydroxamate in Histone Deacetylases Modulated by Water Access to the Linker Binding Channel

Ruibo Wu, Zhenyu Lu, Zexing Cao, and Yingkai Zhang [New York University]

J. Am. Chem. Soc., **133**, 6110–6113, 2011.

It is of significant biological interest and medical importance to develop class- and isoform-selective histone deacetylase (HDAC) modulators. The impact of the linker component on HDAC inhibition specificity has been revealed but is not understood. Using Born–Oppenheimer ab initio QM/MM MD simulations, a state-of-the-art approach to simulating metallo-enzymes, we have found that the hydroxamic acid remains to be protonated upon its binding to HDAC8, and thus disproved the mechanistic hypothesis that the distinct zinc–hydroxamate chelation modes between two HDAC subclasses come from different protonation states of the hydroxamic acid.

Protein-Protein Interactions

pyDockCG: New Coarse-Grained Potential for Protein-Protein Docking

Albert Solernou and Juan Fernandez-Recio [Barcelona Supercomputing Center]

J. Phys. Chem. B., **115**, 6032–6039, 2011.

Protein-protein interactions are fundamental for the majority of biological processes, so their structural, functional, and energetic characterization is of enormous biotechnological and therapeutic interest. In recent years, a variety of computational docking approaches to the structural prediction of protein-protein complexes have been reported, with encouraging results. This work describes pyDockCG, a new coarse-grained potential for protein-protein docking scoring and refinement, based on the known UNRES model for polypeptide chains.

Protein-Protein Interactions: Principles, Techniques, and their Potential Role in New Drug Development

Shagufta H. Khan, Faizan Ahmad, Nihal Ahmad, Daniel C. Flynn, Raj Kumar [The Commonwealth Medical College]

J. Biomol. Stru. and Dyn., **28**, 929-938, 2011.

A vast network of genes is inter-linked through protein-protein interactions and is critical component of almost every biological process under physiological conditions. Proper understanding of biological functions warrants a full knowledge of protein-protein interactions and the molecular mechanisms that govern such processes. We have summarized protein-protein interaction networks, techniques/methods of their binding/kinetic parameters, and the role of these interactions in the development of potential tools for drug designing.

Membrane Proteins and Lipid Peptide Interactions

Virtual screening using molecular simulations

Tianyi Yang, Johnny C. Wu, Chunli Yan, Yuanfeng Wang, Ray Luo, Michael B. Gonzales, Kevin N. Dalby and Pengyu Ren [The University of Texas]

Proteins: Stru. Fun. and Bioinfo. **79**, 1940–1951, 2011.

Effective virtual screening relies on our ability to make accurate prediction of protein-ligand binding, which remains a great challenge. In this work, utilizing the molecular-mechanics Poisson-Boltzmann (or Generalized Born) surface area approach, we have evaluated the binding affinity of a set of 156 ligands to seven families of proteins, trypsin β , thrombin α , cyclin-dependent kinase (CDK), cAMP-dependent kinase (PKA), urokinase-type plasminogen activator, β -glucosidase A, and coagulation factor Xa. The effect of protein dielectric constant in the implicit-solvent model on the binding free energy calculation is shown to be important.

Conformational changes induced by ATP-hydrolysis in an ABC transporter: A molecular dynamics study of the Sav1866 exporter

A. Sofia Oliveira, António M. Baptista and Cláudio M. Soares [Universidade Nova de Lisboa]

Proteins: Stru. Fun. and Bioinfo. **79**, 1977–1990, 2011.

ATP-Binding Cassette (ABC) transporters are ubiquitous membrane proteins that use energy from ATP binding or/and hydrolysis to actively transport allocrites across membranes. In this study, we identify ATP-hydrolysis induced conformational changes in a complete ABC exporter (Sav1866) from *Staphylococcus aureus*, using molecular dynamics (MD) simulations. By performing MD simulations on the ATP and ADP+IP bound states, we identify the conformational consequences of hydrolysis, showing that the major rearrangements are not restricted to the NBDs, but extend to the transmembrane domains (TMDs) external regions.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Orientation of Fluorescent Lipid Analogue BODIPY-PC to Probe Lipid Membrane Properties: Insights from Molecular Dynamics Simulations

Kevin C. Song, Philip W. Livanec, Jeffery B. Klauda, Krzysztof Kuczera, Robert C. Dunn, and Wonpil Im [The University of Kansas]

J. Phys. Chem. B., **115**, 6157–6165, 2011.

Single-molecule fluorescence measurements have been used to characterize membrane properties, and recently showed a linear evolution of the fluorescent lipid analogue BODIPY-PC toward small tilt angles in Langmuir–Blodgett monolayers as the lateral surface pressure is increased. In this work, we have performed comparative molecular dynamics (MD) simulations of BODIPY-PC in DPPC (dipalmitoylphosphatidylcholine) monolayers and bilayers at three surface pressures (3, 10, and 40 mN/m) to explore (1) the microscopic correspondence between monolayer and bilayer structures, (2) the fluorophore's position within the membrane, and (3) the microscopic driving forces governing the fluorophore's tilting.

Anisotropic Solvent Model of the Lipid Bilayer. 1. Parameterization of Long-Range Electrostatics and First Solvation Shell Effects

Andrei L. Lomize [University of Michigan], Irina D. Pogozheva, and Henry I. Mosberg

J. Chem. Infor. and Mod. **51**, 918–929, 2011.

A new implicit solvation model was developed for calculating free energies of transfer of molecules from water to any solvent with defined bulk properties. The transfer energy was calculated as a sum of the first solvation shell energy and the long-range electrostatic contribution. The simplicity and computational efficiency of the model allows its application for modeling of macromolecules in anisotropic environments, such as biological membranes.

Interleaflet Interaction and Asymmetry in Phase Separated Lipid Bilayers: Molecular Dynamics Simulations

Jason D. Perlmutter and Jonathan N. Sachs [University of Minnesota, Minneapolis]

J. Am. Chem. Soc., **133**, 6563–6577, 2011.

In order to investigate experimentally inaccessible, molecular-level detail regarding interleaflet interaction in membranes, we have run an extensive series of coarse-grained molecular dynamics simulations of phase separated lipid bilayers. We have run simulations where the lengths of the saturated lipid chains as well as the mole ratios of the three lipid components are varied. Collectively, we report on three types of interleaflet coupling within a bilayer.

Exploring Peptide-Membrane Interactions with Coarse-Grained MD Simulations

Benjamin A. Hall, Alan P. Chetwynd, Mark S.P. Sansom [University of Oxford]

Biophysical Journal. **100**, 1642–1650, 2011.

The interaction of α -helical peptides with lipid bilayers is central to our understanding of the physicochemical principles of biological membrane organization and stability. Mutations that alter the position or orientation of an α -helix within a membrane, or that change the probability that the α -helix will insert into the membrane, can alter a range of membrane protein functions. We describe a comparative coarse-grained molecular dynamics simulation methodology, based on self-assembly of a lipid bilayer in the presence of an α -helical peptide, which allows us to model membrane transmembrane helix insertion.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Interpretation of Fluctuation Spectra in Lipid Bilayer Simulations

Erik G. Brandt, Anthony R. Braun, Jonathan N. Sachs, John F. Nagle, Olle Edholm [Royal Institute of Technology, Stockholm]

Biophysical Journal. **100**, 2104-2111, 2011.

Atomic resolution and coarse-grained simulations of dimyristoylphosphatidylcholine lipid bilayers were analyzed for fluctuations perpendicular to the bilayer using a completely Fourier-based method. We find that the fluctuation spectrum of motions perpendicular to the bilayer can be decomposed into just two parts: 1), a pure undulation spectrum proportional to q^{-4} that dominates in the small- q regime; and 2), a molecular density structure factor contribution that dominates in the large- q regime.

Determination of Electron Density Profiles and Area from Simulations of Undulating Membranes

Anthony R. Braun, Erik G. Brandt, Olle Edholm, John F. Nagle, Jonathan N. Sachs [University of Minnesota]

Biophysical Journal. **100**, 2112-2120, 2011.

The traditional method for extracting electron density and other transmembrane profiles from molecular dynamics simulations of lipid bilayers fails for large bilayer systems, because it assumes a flat reference surface that does not take into account long wavelength undulations. We have developed what we believe to be a novel set of methods to characterize these undulations and extract the underlying profiles in the large systems. Our approach first obtains an undulation reference surface for each frame in the simulation and subsequently isolates the long-wavelength undulations by filtering out the intrinsic short wavelength modes.

Protein Folding

The ensemble folding kinetics of the FBP28 WW domain revealed by an all-atom Monte Carlo simulation in a knowledge-based potential

Jiabin Xu, Lei Huang and Eugene I. Shakhnovich [Harvard University]

Proteins: Stru. Fun. and Bioinfo. **79**, 1704–1714, 2011.

In this work, we apply a detailed all-atom model with a transferable knowledge-based potential to study the folding kinetics of Formin-Binding protein, FBP28, which is a canonical three-stranded β -sheet WW domain. Replica exchange Monte Carlo simulations starting from random coils find native-like (Ca RMSD of 2.68 Å) lowest energy structure. We also study the folding kinetics of FBP28 WW domain by performing a large number of ab initio Monte Carlo folding simulations.

Equilibrium Distribution from Distributed Computing (Simulations of Protein Folding)

Riccardo Scalco and Amedeo Caflisch [University of Zurich]

J. Phys. Chem. B., **115**, 6358–6365, 2011.

Multiple independent molecular dynamics (MD) simulations are often carried out starting from a single protein structure or a set of conformations that do not correspond to a thermodynamic ensemble. Therefore, a significant statistical bias is usually present in the Markov state model generated by simply combining the whole MD sampling into a network whose nodes and links are clusters of snapshots and transitions between them, respectively. Here, we introduce a depth-first search algorithm to extract from the whole conformation space network the largest ergodic component.

Protein Folding (Cont'd)

Validation of the GROMOS 54A7 Force Field with Respect to β -Peptide Folding

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

J. Chem. Theor. and Comp., **7**, 1237–1243, 2011.

The recently developed GROMOS 54A7 force field, a modification of the 53A6 force field, is validated by simulating the folding equilibrium of two β -peptides which show different dominant folds, i.e., a 3_{14} -helix and a hairpin, using three different force fields, i.e., GROMOS 45A3, 53A6, and 54A7. The 54A7 force field stabilizes both folds, and the agreement of the simulated NOE atom–atom distances with the experimental NMR data is slightly improved when using the 54A7 force field, while the agreement of the ^3J couplings with experimental results remains essentially unchanged when varying the force field.

Microsecond Scale Replica Exchange Molecular Dynamic Simulation of Villin Headpiece: An Insight into the Folding Landscape

Vinod Jani, Uddhaves B. Sonavane, Rajendra Joshi [Pune University Campus]

J. Biomol. Stru. and Dyn., **28**, 845-860, 2011.

Reaching the experimental time scale of millisecond is a grand challenge for protein folding simulations. The development of advanced Molecular Dynamics techniques like Replica Exchange Molecular Dynamics (REMD) makes it possible to reach these experimental timescales. In this study, an attempt has been made to reach the multi microsecond simulation time scale by carrying out folding simulations on a three helix bundle protein, Villin, by combining REMD and Amber United Atom model.

Protein-Nucleic acid Interactions

Specific interactions between lactose repressor protein and DNA affected by ligand binding: Ab initio molecular orbital calculations

Tatsuya Ohyama, Masato Hayakawa, Shin Nishikawa and Noriyuki Kurita [Toyohashi University of Technology]

J. Comp. Chem. **32**, 1661–1670, 2011.

Transcription mechanisms of gene information from DNA to mRNA are essentially controlled by regulatory proteins such as a lactose repressor (LacR) protein and ligand molecules. Biochemical experiments elucidated that a ligand binding to LacR drastically changes the mechanism controlled by LacR, although the effect of ligand binding has not been clarified at atomic and electronic levels. We here investigated the effect of ligand binding on the specific interactions between LacR and operator DNA by the molecular simulations combined with classical molecular mechanics and ab initio fragment molecular orbital methods.

Nucleic Acids

Coarse-Grained Molecular Dynamics Simulation of DNA Translocation in Chemically Modified Nanopores

Abhijit Ramachandran, Qingjiang Guo, Samir M. Iqbal, and Yaling Liu [Lehigh University]

J. Phys. Chem. B., **115**, 6138–6148, 2011.

Solid-state nanopores provide a direct means to detect and analyze DNA and proteins. In a typical setup, the DNA molecules travel through a nanopore under electrophoretic voltage bias. The nanopore is sandwiched between two chambers that are filled with ionic solution. A major challenge in using solid-state nanopores for DNA sequencing and gene detection is to improve their selectivity and detection sensitivity. This paper presents DNA translocation dynamics and the mechanism of DNA sequencing in a functionalized nanopore through a coarse-grained molecular dynamics model.

Electronic and molecular structure of M-DNA fragments

Yury V. Rubin [NAS Ukraine], Leonid F. Belous and Anatolij A. Yakuba

J. Mol.Mod., **17**, 997-1006, 2011.

To study M-DNA molecular structure (such DNA with transition metal ions placed between the nucleic bases is able to conduct the electric current) and its conductivity mechanisms, we carried out ab initio quantum-mechanical calculations of electronic and spatial structures, thermodynamic characteristics of adenine-thymine (AT) and guanine-cytosine (GC) base pair complexes with Zn^{2+} and Ni^{2+} . To take into account the influence of the alkaline environment, calculations for these complexes were also carried out with hydroxyl and two water molecules.

Effect of CpG methylation on DNA binding protein: Molecular dynamics simulations of the homeodomain PITX2 bound to the methylated DNA

Si-Ya Yang, Xiao-Li Yang, Li-Feng Yao, Hai-Bo Wang, Chen-Ke Sun [Qujing Normal University]

J. Mol.Graph. and Mod., **29**, 920-927, 2011.

A large number of studies have argued that aberrant CpG methylation is associated with some human cancers. One possible mechanism of the cancer caused by CpG methylation is the gene repression, which is a binding-inhibition of the sequence-specific transcription factors bound to specific DNA-binding sites. We have performed molecular dynamics (MD) simulations and free energy calculations of the protein bound to the native or the methylated DNA, in which the solution structure of the K50-class homeodomain PITX2 bound to DNA was used as a template.

Theoretical design of a specific DNA–Zinc-finger protein interaction with semi-empirical quantum chemical methods

Gábor Nagy, Béla Gyurcsik, Eufrozina A. Hoffmann, Tamás Körtvélyesi [University of Szeged]

J. Mol.Graph. and Mod., **29**, 928-934, 2011.

The interactions of a zinc-finger (ZF) protein with DNA containing the specific recognition site of the ZF and with a non-specific DNA were studied with the semi-empirical quantum chemical method of PM6/Mozyme. The ZF protein (1MEY)-DNA complex structures were generated by docking calculations. The complex structures were reoptimized with the PM6/Mozyme method with implicit solvation in water. The structures were also calculated in the gas phase.

Nucleic Acids (Cont'd)

Iso-energetic multiple conformations of hypermodified nucleic acid base wybutine (yW) which occur at 37th position in anticodon loop of tRNA^{Phe}

Navanath M. Kumbhar, Kailas D. Sonawane [Shivaji University]

J. Mol. Graph. and Mod., **29**, 935-946, 2011.

Conformational preferences of wybutine (yW) have been studied by quantum chemical semi-empirical Perturbative Configuration Interaction with Localized Orbitals (PCILO) and PM3 methods. Automated full geometry optimization by using RM1 along with ab-initio Hartree-Fock (HF-SCF) and Density Functional Theory (B3LYP/6-31G**) calculations have also been made to compare the salient features. Molecular dynamics (MD) simulation has been performed to see the solvation effect on wybutine side chain.

Impact of 2'-hydroxyl sampling on the conformational properties of RNA: Update of the CHARMM all-atom additive force field for RNA

Elizabeth J. Denning, U. Deva Priyakumar, Lennart Nilsson and Alexander D. Mackerell Jr. [University of Maryland]

J. Comp. Chem. **32**, 1929–1943, 2011.

Here, we present an update of the CHARMM27 all-atom additive force field for nucleic acids that improves the treatment of RNA molecules. The original CHARMM27 force field parameters exhibit enhanced Watson-Crick base pair opening which is not consistent with experiment, whereas analysis of molecular dynamics (MD) simulations show the 2'-hydroxyl moiety to almost exclusively sample the O3' orientation. Quantum mechanical (QM) studies of RNA related model compounds indicate the energy minimum associated with the O3' orientation to be too favorable, consistent with the MD results.

Blocking the DNA Repair System by Traditional Chinese Medicine?

Mao-Feng Sun, Tung-Ti Chang, Kai-Wei Chang, Hung-Jin Huang, Hsin-Yi Chen, Fuu-Jen Tsai, Jaung-Geng Lin, Calvin Yu-Chian Chen [China Medical University]

J. Biomol. Stru. and Dyn., **28**, 895-906, 2011.

Non-homologous end joining (NHEJ) is a major DNA double strand breaks (DSBs) repair pathway that maintains genome integrity. However, this pathway may reduce radiotherapy efficacy by repairing DSBs on cancer cells. This research reported a computer-aided drug design (CADD) method to identify novel inhibitors from traditional Chinese medicine (TCM) that disrupt NHEJ. We aim to inhibit Ku86, the initiator of NHEJ. By integrating binding energy evaluation and molecular dynamics simulation methods, we reported glycyrrhizic acid, macedonoside C, lithospermic acid, and salvianolic acid B as potential Ku86 inhibitors.

Surfaces, Catalysts, and Materials Subjects

2. METHODOLOGY

Potentials and Parameters

Polarizable Simulations with Second-Order Interaction Model (POSSIM) Force Field: Developing Parameters for Alanine Peptides and Protein Backbone

Sergei Y. Ponomarev and George A. Kaminski [Worcester Polytechnic Institute]

J. Chem. Theor. and Comp., **7**, 1415–1427, 2011.

Polarizable simulations with second-order interaction model (POSSIM) force field has been extended to include parameters for alanine peptides and protein backbones. New features were introduced into the fitting protocol, as compared to the previous generation of the polarizable force field for proteins. A reduced amount of quantum mechanical data was employed in fitting the electrostatic parameters. Transferability of the electrostatics between our recently developed N-methylacetamide model and the protein backbone was confirmed.

Modification of Martini force field for molecular dynamics simulation of hydrophobic charge induction chromatography of lysozyme

Lin Zhang, Shu Bai, Yan Sun [Tianjin University]

J. Mol. Graph. and Mod., **29**, 906-914, 2011.

Modeling, especially the force field, is crucial for the accuracy of molecular dynamics (MD) simulations. In order for more accurate description of adsorption and desorption behaviors of lysozyme in hydrophobic charge induction chromatography (HCIC), the Martini coarse-grained (CG) force field has been modified based on the statistical analysis and comparison of an all-atom (AA) force field, GROMOS96 43A1, and the Martini force field. The parameters describing the protein-adsorbent interactions have been adjusted to avoid too strong and unrealistic adsorption of lysozyme on the agarose matrix and HCIC ligands.

Optimization of parameters for molecular dynamics simulation using smooth particle-mesh Ewald in GROMACS 4.5

Mark J. Abraham and Jill E. Gready [Australian National University]

J. Comp. Chem. **32**, 2031–2040, 2011.

Based on our critique of requirements for performing an efficient molecular dynamics simulation with the particle-mesh Ewald (PME) implementation in GROMACS 4.5, we present a computational tool to enable the discovery of parameters that produce a given accuracy in the PME approximation of the full electrostatics. Calculations on two parallel computers with different processor and communication structures showed that a given accuracy can be attained over a range of parameter space, and that the attributes of the hardware and simulation system control which parameter sets are optimal.

How Robust Are Protein Folding Simulations with Respect to Force Field Parameterization?

Stefano Piana, Kresten Lindorff-Larsen, David E. Shaw [D. E. Shaw Research]

Biophysical Journal. **100**, L47-L49, 2011.

Molecular dynamics simulations hold the promise of providing an atomic-level description of protein folding that cannot easily be obtained from experiments. Here, we examine the extent to which the molecular mechanics force field used in such simulations might influence the observed folding pathways. To that end, we performed equilibrium simulations of a fast-folding variant of the villin headpiece using four different force fields.

Potentials and Parameters (Cont'd)

Direct Observations of Shifts in the β -Sheet Register of a Protein-Peptide Complex Using Explicit Solvent Simulations

Maria T. Panteva, Reza Salari, Monica Bhattacharjee, Lillian T. Chong [University of Pittsburgh]

Biophysical Journal. **100**, L50-L52, 2011.

Using explicit solvent molecular dynamics simulations, we were able to obtain direct observations of shifts in the hydrogen-bonding register of an intermolecular β -sheet protein-peptide complex. The β -sheet is formed between the FHA domain of cancer marker protein Ki67 (Ki67FHA) and a peptide fragment of the hNIFK signaling protein. Potential encounter complexes of the Ki67FHA receptor and hNIFK peptide are misregistered states of the β -sheet. Rearrangements of one of these misregistered states to the native state were captured in three independent simulations.

Molecular Dynamics

Boxed Molecular Dynamics: Decorrelation Time Scales and the Kinetic Master Equation

David R. Glowacki, Emanuele Paci, and Dmitrii V. Shalashilin [University of Bristol]

J. Chem. Theor. and Comp, **7**, 1244–1252, 2011.

A number of methods proposed in the past few years have been aimed at accelerating the sampling of rare events in molecular dynamics simulations. We recently introduced a method called Boxed Molecular Dynamics (BXD) for accelerating the calculation of thermodynamics and kinetics (*J. Phys. Chem. B* 2009, 113, 16603–16611). BXD relies upon confining the system in a series of adjacent “boxes” by inverting the projection of the system velocities along the reaction coordinate.

Keep It Flexible: Driving Macromolecular Rotary Motions in Atomistic Simulations with GROMACS

Carsten Kutzner [Max Planck Institute for Biophysical Chemistry], Jacek Czub, and Helmut Grubmüller

J. Chem. Theor. and Comp, **7**, 1381–1393, 2011.

We describe a versatile method to enforce the rotation of subsets of atoms, e.g., a protein subunit, in molecular dynamics (MD) simulations. In particular, we introduce a “flexible axis” technique that allows realistic flexible adaptations of both the rotary subunit as well as the local rotation axis during the simulation. A variety of useful rotation potentials were implemented for the GROMACS 4.5 MD package. Application to the molecular motor F₁-ATP synthase demonstrates the advantages of the flexible axis approach over the established fixed axis rotation technique.

QM and QM/MM

Molecules-in-Molecules: An Extrapolated Fragment-Based Approach for Accurate Calculations on Large Molecules and Materials

Nicholas J. Mayhall and Krishnan Raghavachari [Indiana University]

J. Chem. Theor. and Comp, **7**, 1336–1343, 2011.

We present a new extrapolated fragment-based approach, termed molecules-in-molecules (MIM), for accurate energy calculations on large molecules. In this method, we use a multilevel partitioning approach coupled with electronic structure studies at multiple levels of theory to provide a hierarchical strategy for systematically improving the computed results. In particular, we use a generalized hybrid energy expression, similar in spirit to that in the popular ONIOM methodology, that can be combined easily with any fragmentation procedure.

QM and QM/MM (Cont'd)

Modeling Fast Electron Dynamics with Real-Time Time-Dependent Density Functional Theory: Application to Small Molecules and Chromophores

Kenneth Lopata [Pacific Northwest National Laboratory] and Niranjan Govind

J. Chem. Theor. and Comp., **7**, 1344–1355, 2011.

The response of matter to external fields forms the basis for a vast wealth of fundamental physical processes ranging from light harvesting to nanoscale electron transport. Accurately modeling ultrafast electron dynamics in excited systems thus offers unparalleled insight but requires an inherently nonlinear time-resolved approach. To this end, an efficient and massively parallel real-time real-space time-dependent density functional theory (RT-TDDFT) implementation in NWChem is presented.

Conformations Consistent with Charge Migration Observed in DNA and RNA X-ray Structures

Marianne Rooman [Université Libre de Bruxelles], Emilie Cauët, Jacques Liévin, René Wintjens

J. Biomol. Stru. and Dyn., **28**, 949- 953, 2011.

Electron holes are known to migrate along the DNA or RNA duplexes and to localize preferentially on successive guanines. The stationary point conformations of Gua pairs that can trap or let pass these holes have been characterized by quantum chemistry calculations. Here we show their recurrent occurrence in DNA and RNA X-ray structures, often in quadruplex conformations or in interaction with proteins, ligands or metal ions. These findings give support to the biological, possibly regulatory, roles of charge migration in cell functioning.

Compounds of the 1,5-di(4-R-phenyl)-3-selenopentanediones-1,5 series interaction with the Basidiomycete Lentinula edodes lectins: Computations and Experiment

Alexei N. Pankratov, Olga M. Tsivileva [RAS, 13 Entuziastov Ave.], Boris I. Drevko, Valentina E. Nikitina

J. Biomol. Stru. and Dyn., **28**, 969-974, 2011.

The role of spatial and electron structure, hydrophobic properties and concentration of organoselenium compounds on their interaction with fungal metabolites - extracellular lectins of Lentinula edodes (shiitake mushroom) has been considered. By the hybrid method of density functional theory at the B3LYP/6-31G(d,p) theory level, spatial and electronic structure of the 1,5-diphenyl-3-selenopentanedione-1,5 (preparation DAPS-25), 1,5-di(4-methoxyphenyl)-3-selenopentanedione-1,5 and 1,5-di(4-ethoxyphenyl)-3-selenopentanedione-1,5 molecules has been studied.

Comparative or Homology Modeling

Exploring the structure of opioid receptors with homology modeling based on single and multiple templates and subsequent docking: A comparative study

Indrani Bera, Aparna Laskar and Nanda Ghoshal [Indian Institute of Chemical Biology, Kolkata]

J. Mol.Mod., **17**, 1207-1221, 2011.

Opioid receptors are the principal targets for opioids, which have been used as analgesics for centuries. Opioid receptors belong to the rhodopsin family of G-protein coupled receptors (GPCRs). In the absence of crystal structures of opioid receptors, 3D homology models have been reported with bovine rhodopsin as a template, though the sequence homology is low. With the objective of carrying out a comparative study on the structural quality of the 3D models based on single and multiple templates, the homology models for opioid receptors (μ , δ and κ) were generated using bovine rhodopsin as single template and the recently deposited crystal structures of squid rhodopsin, turkey β -1 and human β -2 adrenoreceptors along with bovine rhodopsin as multiple templates.

Ligand Docking

Molecular dynamics simulations reveal structural coordination of Ffh-FtsY heterodimer toward GTPase activation

Ming-Jun Yang and Xin Zhang [The Scripps Research Institute]

Proteins: Stru. Fun. and Bioinfo. **79**, 1774–1785, 2011.

Two homologous GTPases (guanine-triphosphatases) in the signal recognition particle (SRP) and its receptor (SR) use their cumulative energy during GTP (guanine-triphosphate) hydrolysis to control the co-translational protein targeting process. Here, we examined the stability and dynamics of three interaction networks involving these residues and discovered that they contribute to the GTPase activation via well-tuned conformational changes. The crystallographically identified pending residues Ffh:R191/FtsY:R195 undergo extensive conformational rearrangements to form persisted interactions with FtsY:E284/Ffh:E274, explaining the biochemically observed defective effect of R191 mutant to the activation of both GTPases.

Binding Ligands and Cofactor to L-Lactate Dehydrogenase from Human Skeletal and Heart Muscles

Katarzyna Swiderek [Technical University of Lodz] and Piotr Paneth

J. Phys. Chem. B., 115, 6366–6376, 2011.

Binding affinities of cofactor and ligands to the active site of two different isoforms of lactate dehydrogenase (LDH), heart and skeletal muscles (H4 and M4, respectively), can be used for medical and biological applications. Herein, a hybrid QM/MM computational approach based on free energy perturbation methods has been carried out to estimate binding affinities and binding isotope effects (BIEs) for NADH/NAD⁺ and oxamate, pyruvate, L-lactate, and D-lactate ligands to the M4 and H4 isoforms of L-LDH. Here, we show that determining how cofactor and ligands interact with the active site of LDH isoforms advanced the still open discussion on the intracellular lactate shuttle hypothesis.

Accelerating Molecular Docking Calculations Using Graphics Processing Units

Oliver Korb [Cambridge Crystallographic Data Centre], Thomas Stotzle, and Thomas E. Exner

J.Chem. Infor. and Mod. **51**, 865–876, 2011.

The generation of molecular conformations and the evaluation of interaction potentials are common tasks in molecular modeling applications, particularly in protein–ligand or protein–protein docking programs. In this work, we present a GPU-accelerated approach capable of speeding up these tasks considerably. For the evaluation of interaction potentials in the context of rigid protein–protein docking, the GPU-accelerated approach reached speedup factors of up to over 50 compared to an optimized CPU-based implementation.

Reproducing Crystal Binding Modes of Ligand Functional Groups Using Site-Identification by Ligand Competitive Saturation (SILCS) Simulations

E. Prabhu Raman, Wenbo Yu, Olgun Guvench, and Alexander D. MacKerell, Jr. [University of Maryland School of Pharmacy]

J.Chem. Infor. and Mod. **51**, 877–896, 2011.

The applicability of a computational method, Site Identification by Ligand Competitive Saturation (SILCS), to identify regions on a protein surface with which different types of functional groups on low-molecular weight inhibitors interact is demonstrated. The method involves molecular dynamics (MD) simulations of a protein in an aqueous solution of chemically diverse small molecules from which probability distributions of fragments types, termed FragMaps, are obtained.

Ligand Docking (Cont'd)

Molecular Docking with Ligand Attached Water Molecules

Mette A. Lie [Aarhus University], Rene Thomsen, Christian N. S. Pedersen, Birgit Schiøtt, and Mikael H. Christensen

J.Chem. Infor. and Mod. **51**, 909–917, 2011.

A novel approach to incorporate water molecules in protein–ligand docking is proposed. In this method, the water molecules display the same flexibility during the docking simulation as the ligand. The method solvates the ligand with the maximum number of water molecules, and these are then retained or displaced depending on energy contributions during the docking simulation. Instead of being a static part of the receptor, each water molecule is a flexible on/off part of the ligand and is treated with the same flexibility as the ligand itself.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 29(7), June, 2011.

895-905 **dxTuber: Detecting protein cavities, tunnels and clefts based on protein and solvent dynamics**, Martin Raunest, Christian Kandt [University of Bonn]

See Applications / Protein Dynamics.

906-914 **Modification of Martini force field for molecular dynamics simulation of hydrophobic charge induction chromatography of lysozyme**, Lin Zhang, Shu Bai, Yan Sun [Tianjin University]

See Methodology / Potentials and Parameters.

915-919 **Computational study on the interaction of a ring-hydroxylating dioxygenase from *Sphingomonas* CHY-1 with PAHs**, Vito Librando [Università di Catania], Matteo Pappalardo

See Applications / Enzyme Catalysis.

920-927 **Effect of CpG methylation on DNA binding protein: Molecular dynamics simulations of the homeodomain PITX2 bound to the methylated DNA**, Si-Ya Yang, Xiao-Li Yang, Li-Feng Yao, Hai-Bo Wang, Chen-Ke Sun [Qufu Normal University]

See Applications / Nucleic Acids.

928-934 **Theoretical design of a specific DNA–Zinc-finger protein interaction with semi-empirical quantum chemical methods**, Gábor Nagy, Béla Gyurcsik, Eufrozina A. Hoffmann, Tamás Körtvélyesi [University of Szeged]

See Applications / Nucleic Acids.

935-946 **Iso-energetic multiple conformations of hypermodified nucleic acid base wybutine (yW) which occur at 37th position in anticodon loop of tRNA^{Phe}**, Navanath M. Kumbhar, Kailas D. Sonawane [Shivaji University]

See Applications / Nucleic Acids.

947-955 **Molecular modelling and competition binding study of Br-noscapine and colchicine provide insight into noscapinoid–tubulin binding site**, Pradeep K. Naik, Seneka Santoshi, Ankit Rai, Harish C. Joshi [Emory University School of Medicine]

See Applications / Ligand Binding.

- 956-964 **Binding modes of diketo-acid inhibitors of HIV-1 integrase: A comparative molecular dynamics simulation study**, Meilan Huang [Queens University Belfast], Guy H. Grant, W. Graham Richards

See Applications / Protein Dynamics.

- 965-973 **Novel ligands that target the mitochondrial membrane protein mitoNEET**, Robert M. Bieganski, Martin L. Yarmush [Harvard Medical School]

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 32(8), June, 2011.

- 1493–1499 **Testing the ONIOM G2R3 model against donor–acceptor dissociation energies of group 13–15 complexes: Accuracy comparable to CCSD(T)/aug-CC-pVTZ at a fraction of the resource cost**, Thomas M. Gilbert [Northern Illinois University]

The ability of the composite three-layer ONIOM G2R3 (OG2R3) method to match experimental dissociation energies for group 13–15 donor–acceptor complexes was examined for a database of 34 complexes.

- 1500–1518 **Vibrational spectral signatures of peptide secondary structures: N-methylation and side chain hydrogen bond in cyclosporin A**, Zheng-Wang Qu [Humboldt Universität zu Berlin], Hui Zhu and Volkhard May

See Applications / Medicinal Chemistry and Drug Design.

- 1519–1527 **A comparison of the behavior of functional/basis set combinations for hydrogen-bonding in the water dimer with emphasis on basis set superposition error**, Joshua A. Plumley and J. J. Dannenberg [City University of New York]

We evaluate the performance of ten functionals (B3LYP, M05, M05-2X, M06, M06-2X, B2PLYP, B2PLYPD, X3LYP, B97D, and MPWB1K) in combination with 16 basis sets ranging in complexity from 6-31G(d) to aug-cc-pV5Z for the calculation of the H-bonded water dimer with the goal of defining which combinations of functionals and basis sets provide a combination of economy and accuracy for H-bonded systems.

- 1528–1540 **Electron localization function and electron localizability indicator applied to study the bonding in the peroxyxynitrous acid HOONO**, Slawomir Berski [University of Wroclaw], Zdzislaw Latajka and Agnieszka J. Gordon

The ground-state electronic structure of peroxyxynitrous acid (HOONO) and its singlet biradicaloid form (HO $\cdots$ ONO) have been studied using topological analysis of the electron localization function (ELF), together with the electron localizability indicator (ELI-D), at the DFT (B3LYP, M05, M052X, and M06), CCSD, and CASSCF levels.

- 1541–1549 **Conformational searching using a population-based incremental learning algorithm**, Stephen M. Long, Tran T. Tran, Peter Adams, Paul Darwen and Mark L. Smythe [The University of Queensland]

A new population-based incremental learning algorithm for conformational searching of molecules is presented.

- 1550–1560 **The shape of gaseous n-butylbenzene: Assessment of computational methods and comparison with experiments**, Stéphanie Halbert, Carine Clavaguéra and Guy Bouchoux [Ecole Polytechnique et CNRS]

Conformational landscape of neutral and ionized n-butylbenzene has been examined.

- 1561–1567 **A self-consistent Hirshfeld method for the atom in the molecule based on minimization of information loss**, Dieter Ghillemijn, Patrick Bultinck [Ghent University Krijgslaan 281 (S3)], Dimitri Van Neck and Paul W. Ayers

Based on the so-called Hirshfeld atom in the molecule scheme, a new AIM method is presented. The method is similar to the Hirshfeld-I scheme, with the AIM weight function being constructed by minimizing the information loss upon formation of the molecule, but now requiring explicitly that the promolecular densities integrate to the same number of electrons as the AIM densities.

- 1568–1576 **Theoretical investigation of novel carbazole-fluorene based D- π -A conjugated organic dyes as dye-sensitizer in dye-sensitized solar cells (DSCs)**, Thanisorn Yakhanthip, Siriporn Jungsuttiwong [Ubon Ratchathani University], Supawadee Namuangruk, Nawe Kungwan, Vinich Promarak, Taweesak Sudyoadsuk and Palita Kochpradist

The ground state structure and frontier molecular orbital of newly synthesized carbazole-fluorene based D- π -A organic dyes, CFP1A, CFP2A, CFP1CA, and CFP2CA, were theoretically investigated using density functional theory (DFT) at B3LYP/6-31G(d,p) level.

- 1577–1588 **Extensive theoretical study on electronically excited states and predissociation mechanisms of sulfur monoxide including spin-orbit coupling**, Le Yu and Wensheng Bian [Chinese Academy of Sciences]

The potential energy curves of the 69 Ω states generated from the 24 Λ -S states of sulfur monoxide are calculated for the first time using the internally contracted multireference configuration interaction method with the Davidson correction and the entirely uncontracted aug-cc-pV5Z basis set.

- 1589–1598 **Fast construction of assembly trees for molecular graphs**, Svetlana Artemova [INRIA Grenoble—Rhône-Alpes Research Center], Sergei Grudinin and Stephane Redon

A number of modeling and simulation algorithms using internal coordinates rely on hierarchical representations of molecular systems. Given the potentially complex topologies of molecular systems, though, automatically generating such hierarchical decompositions may be difficult. In this article, we present a fast general algorithm for the complete construction of a hierarchical representation of a molecular system.

- 1599–1611 **The ring current model of the pentaprismane molecule**, Stefano Pelloni, Raphaël Carion [Facultés Universitaires Notre-Dame de la Paix], Vincent Liégeois and Paolo Lazzeretti

Three-dimensional models of the quantum-mechanical current density $\mathbf{J}^B$, induced in the electron cloud of the $C_{10}H_{10}$ pentaprismane molecule by a magnetic field $\mathbf{B}$ applied along the C_5 (a C_2) symmetry axis, orthogonal to the pentagonal (a rectangular) face, and denoted by $\mathbf{B}_\square$ ($\mathbf{B}_\square$), have been constructed.

- 1612–1617 **Predicting protein folding rates using the concept of Chou's pseudo amino acid composition**, Jianxiu Guo, Nini Rao [University of Electronic Science and Technology of China], Guangxiong Liu, Yong Yang and Gang Wang

One of the most important challenges in computational and molecular biology is to understand the relationship between amino acid sequences and the folding rates of proteins. In this study, amino acid sequence order was used to derive an effective method, based on an extended version of the pseudo-amino acid composition, for predicting protein folding rates without any explicit structural information.

- 1618–1634 **Pharmacophore alignment search tool: Influence of the third dimension on text-based similarity searching**, Volker Hähnke, Alexander Klenner, Friedrich Rippmann and Gisbert Schneider [Swiss Federal Institute of Technology (ETH) Zurich]

Previously (Hähnke et al., J Comput Chem 2010, 31, 2810) we introduced the concept of nonlinear dimensionality reduction for canonization of two-dimensional layouts of molecular graphs as foundation for text-based similarity searching using our Pharmacophore Alignment Search Tool (PhAST), a ligand-based virtual screening method. Here we apply these methods to three-dimensional molecular conformations and investigate the impact of these additional degrees of freedom on virtual screening performance and assess differences in ranking behavior.

- 1635–1647 **Pharmacophore alignment search tool: Influence of scoring systems on text-based similarity searching**, Volker Hähnke and Gisbert Schneider [Swiss Federal Institute of Technology (ETH) Zurich]

See Applications / Medicinal Chemistry and Drug Design.

- 1648–1660 **Franck–Condon simulation of the photoelectron spectrum of $AsCl_2$ and the photodetachment**

spectrum of $AsCl$ employing UCCSD(T)-F12a potential energy functions: IE and EA of $AsCl_2$, Daniel K. W. Mok [Hong Kong Polytechnic University], Edmond P. F. Lee, Foo-Tim Chau and John M. Dyke

The currently most reliable theoretical estimates of the adiabatic ionization energies (AIE_0) from the $\tilde{X}^2B_1$ state of $AsCl_2$ to the $\tilde{X}^1A_1$ and $\tilde{a}^3B_1$ states of $AsCl_2^+$, and the electron affinity (EA_0) of $AsCl_2$, including ΔZPE corrections, are calculated as 8.687(11), 11.320(23), and 1.845(12) eV, respectively (estimated uncertainties based on basis-set effects at the RCCSD(T) level).

- 1661–1670 **Specific interactions between lactose repressor protein and DNA affected by ligand binding: Ab initio molecular orbital calculations**, Tatsuya Ohyama, Masato Hayakawa, Shin Nishikawa and Noriyuki Kurita [Toyohashi University of Technology]

See Applications / Protein – Nucleic Acids Interactions.

- 1671–1679 **Infinite basis set extrapolation for double hybrid density functional theory 1: Effect of applying various extrapolation functions**, Yao-Yuan Chuang [National University of Kaohsiung] and Sheng-Min Chen

We applied the Infinite Basis (IB) set extrapolation and Double Hybrid Density Functional Theory (DHDF) to calculate the databases of atomization energies, ionization energies, electron affinities, reaction barrier heights, proton affinities, alkyl bond dissociation energies, and noncovalent interactions.

- 1680–1686 **Protein side chain modeling with orientation-dependent atomic force fields derived by series expansions**, Shide Liang [Osaka University], Yaoqi Zhou, Nick Grishin and Daron M. Standley

We describe the development of new force fields for protein side chain modeling called optimized side chain atomic energy (OSCAR).

- 1687–1693 **Can the transition from tunneling to hopping in molecular junctions be predicted by theoretical calculation?**, Hongmei Liu, Zhenzhen Zhao, Nan Wang, Cui Yu and Jianwei Zhao [Nanjing University]

The electron transport mechanism changes from tunneling to hopping as molecular length increases. To validate the theoretical simulation after the transition point and clarify influence of electronic structures on the transition, we calculated the conductance of a series of conjugated molecules by density functional theory together with the nonequilibrium Green's function.

- 1694–1702 **New ab initio potential energy surfaces for both the ground ($\tilde{X}^1A'$) and excited ($\tilde{A}^1A''$) electronic states of HSiCl and the absorption and emission spectra of HSiCl/DSiCl**, Sen Lin and Daiqian Xie [Nanjing University]

New ab initio potential energy surfaces for the ground ($\tilde{X}^1A'$) and excited ($\tilde{A}^1A''$) electronic states of HSiCl were obtained by using the single and double excitation coupled-cluster theory with a noniterative perturbation treatment of triple excitations and the multi-reference configuration interaction with Davidson correction, respectively, employing an augmented correlation-consistent polarized valence quadruple zeta basis set.

- 1703–1710 **Optimization of a molecular mechanics force field for type-II polyoxometalates focussing on electrostatic interactions: A case study**, Blandine Courcot [The University of Sydney] and Adam J. Bridgeman

In this study, we have focussed on type-II polyanions such as $[M_7O_{24}]^{6-}$, and we have developed and validated optimized force fields that include electrostatic and van der Waals interactions.

- 1711–1720 **Force fields for metallic clusters and nanoparticles**, Nicole Legenski, Chenggang Zhou, Qingfan Zhang, Bo Han, Jinping Wu, Liang Chen, Hansong Cheng [China University of Geosciences] and Robert C. Forrey

Atomic force fields for simulating copper, silver, and gold clusters and nanoparticles are developed. Potential energy functions are obtained for both monatomic and binary metallic systems using an embedded atom method.

- 1721–1724 **Modeling the electron density kernels**, Paweł Szarek and Ludwik Komorowski [Wrocław University of Technology]

Existing approximation to the softness kernel, successfully explored in earlier work, has been extended; the normal Gauss distribution function has been used instead of the Dirac delta.

- 1725–1733 **Rate constants for hydrogen abstraction reactions by the hydroperoxyl radical from methanol, ethenol, acetaldehyde, toluene, and phenol**, Mohammednoor Altarawneh [Al-Hussein Bin Talal University], Ala'A H. Al-Muhtaseb, Bogdan Z. Dlugogorski, Eric M. Kennedy and John C. Mackie

An important step in the initial oxidation of hydrocarbons at low to intermediate temperatures is the abstraction of H by hydroperoxyl radical (HO_2). In this study, we calculate energy profiles for the sequence: reactant + $\text{HO}_2 \rightarrow$ [complex of reactants] $\rightarrow$ transition state $\rightarrow$ [complex of products] $\rightarrow$ product + H_2O_2 for methanol, ethenol (i.e., $\text{C}_2\text{H}_3\text{OH}$), acetaldehyde, toluene, and phenol.

- 1734–1742 **Structural, electronic, bonding, and elastic properties of NH_3BH_3 : A density functional study**, Ch. Bheema Lingam, K. Ramesh Babu, Surya P. Tewari and G. Vaitheeswaran [University of Hyderabad]

The structural, electronic, bonding, and elastic properties of the low-temperature orthorhombic phase of NH_3BH_3 are studied by means of first-principles total energy calculations based on the pseudopotential method.

- 1743–1752 **A challenging system: Free energy prediction for factor Xa**, Hannes G. Wallnoefer, Klaus R. Liedl [University of Innsbruck] and Thomas Fox

Factor Xa (fXa) is a promising target for antithrombotic drugs. Recently, we presented a molecular dynamics study on fXa, which highlighted the need for a careful system setup to obtain stable simulations. Here, we show that these simulations can be used to predict the free energy of binding of several fXa inhibitors.

- 1753–1759 **The finite-size effect on the transport properties in edge-modified graphene nanoribbon-based molecular devices**, Zongling Ding, Jun Jiang, Huaizhong Xing, Haibo Shu, Yan Huang, Xiaoshuang Chen [Chinese Academy of Sciences] and Wei Lu

The size-dependence on the electronic and transport properties of the molecular devices of the edge-modified graphene nanoribbon (GNR) slices is investigated using density-functional theory and Green's function theory.

- 1760–1768 **Isomers and isomerization reactions of four nitro derivatives of methane**, Chaoyang Zhang, Xiaolin Wang and Mingfei Zhou [Fudan University]

The nitro, nitrite, and aci-form isomers and the isomerization reactions of mono-, di-, tri-, and tetra-nitromethanes (NMs) were computationally investigated.

Journal of Computational Chemistry, 32(9), July, 2011.

- 1775–1784 **Performance of six functionals (LDA, PBE, PBESOL, B3LYP, PBE0, and WC1LYP) in the simulation of vibrational and dielectric properties of crystalline compounds. The case of forsterite Mg_2SiO_4** , M. De La Pierre [Università di Torino], R. Orlando, L. Maschio, K. Doll, P. Ugliengo and R. Dovesi

The performance of six different density functionals (LDA, PBE, PBESOL, B3LYP, PBE0, and WC1LYP) in describing the infrared spectrum of forsterite, a crystalline periodic system with orthorhombic unit cell (28

atoms in the primitive cell, Pbm space group), is investigated by using the periodic ab initio CRYSTAL09 code and an all-electron Gaussian-type basis set.

- 1785–1800 **A new hybrid algorithm for finding the lowest minima of potential surfaces: Approach and application to peptides**, Moshe Goldstein [The Hebrew University of Jerusalem], Erick Fredj and R. Benny Gerber

A new algorithm is presented for finding the global minimum, and other low-lying minima, of a potential energy surface (PES) of biological molecules.

- 1801–1812 **Calculation of binding free energies of inhibitors to plasmepsin II**, Denise Steiner, Chris Oostenbrink, François Diederich, Martina Zürcher and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich]

See Applications / Free Energy Calculations.

- 1813–1823 **Enantioselective organocatalytic diels–Alder reactions: A density functional theory and kinetic isotope effects study**, Nasr Y.M. Omar, Noorsaadah A. Rahman and Sharifuddin MD Zain [University of Malaya]

The mechanism and enantioselectivity of the organocatalytic Diels–Alder reaction were computationally investigated by density functional theory at the B3LYP/6-31G(d) level of theory.

- 1824–1838 **Accurate bond dissociation enthalpies by using doubly hybrid XYG3 functional**, Igor Ying Zhang, Jianming Wu, Yi Luo and Xin Xu [Xiamen University]

In this work, we examine the performance of XYG3, a newly developed doubly hybrid density functional (Zhang, Xu, and Goddard III, Proc Natl Acad Sci USA 2009, 106, 4963), to calculate covalent bond dissociation enthalpy (BDE).

- 1839–1845 **Accurate quantum-chemical description of gold complexes with pyridine and its derivatives**, Doreen Mollenhauer [Freie Universität Berlin], Johannes Flob, Hans-Ulrich Reissig, Elena Voloshina and Beate Paulus

Interaction of gold with pyridine and its derivatives was studied by means of different wavefunction-based correlation methods and standard DFT functionals as well as accounting for dispersion correction.

- 1846–1858 **An ab initio molecular orbital study of intramolecular hydrogen bonding in ortho-substituted arylamides: Implications for the parameterization of molecular mechanics force fields**, Zhiwei Liu, Alexey Teslja and Vojislava Pophristic [University of the Sciences in Philadelphia]

The aromatic oligoamide (arylamide) foldamer class, characterized by the repetitive aromatic-amide pattern, is one of the most intensively studied foldamer families. In this article, the potential energy profiles with regard to torsional motions around the two types of aromatic-amide bonds (C_a-C_p and C_a-N) are obtained at the B3LYP/6-311G(d,p) level of theory.

- 1859–1868 **Electronic and chelation effects on the unusual C2-methylation of N-(para-substituted)phenylaziridines with lithium organocuprates**, Jongtaek Kim, Eunjung Yoo, Sukbok Chang and Yoon Sup Lee [Korea Advanced Institute of Science and Technology]

Density functional theory calculations with the B3LYP functional were performed for the title ring-opening reaction to understand the intrinsic activating and directing effects of the N-substituents, as well as the electron donating effect of the para-substituted (Y = Cl, H, Me) phenyl group at the more hindered benzylic C2 atom.

- 1869–1875 **Efficiency of random search procedures along the silicon cluster series: Si_n ($n = 5\text{--}10, 15$, and 20),** Fabrice Avaltroni and Clemence Corminboeuf [Ecole Polytechnique Fédérale de Lausanne]

The efficiency of the simplest isomeric search procedure consisting in random generation of sets of atomic coordinates followed by density functional theory geometry optimization is tested on the silicon cluster series ($\text{Si}_{5\text{--}10,15,20}$).

- 1876–1886 **Effect of Na^+ , Mg^{2+} , and Zn^{2+} chlorides on the structural and thermodynamic properties of water/n-heptane interfaces,** Francisco Rodríguez-Ropero and Marco Fioroni [RWTH Aachen University]

The effect on the structural and thermodynamic properties in water/n-heptane interfaces on addition of NaCl, MgCl_2 , and ZnCl_2 has been examined through five independent 100-ns molecular dynamics simulations.

- 1887–1895 **Physical origins of the stability of aromatic amino acid core ring-polycyclic hydrocarbon complexes: A post-Hartree-fock and density functional study,** Żaneta Czyżnikowska [Wrocław Medical University] and Wojciech Bartkowiak

Noncovalent interactions between four aromatic amino acid core rings and polycyclic hydrocarbons (up to 58 carbon atoms) were investigated at the post-Hartree-Fock level of theory and with the aid of the density functional theory.

- 1896–1906 **A computational study of the reactivities of four-membered heavy carbene systems,** Chi-Shiun Wu and Ming-Der Su [National Chiayi University]

The potential energy surfaces for the chemical reactions of four-membered N-heterocyclic group 14 heavy carbene species have been studied using density functional theory (B3LYP/LANL2DZ).

- 1907–1918 **Role of bridging water molecules in GSK3 β -inhibitor complexes: Insights from QM/MM, MD, and molecular docking studies,** Shao-Yong Lu, Yong-Jun Jiang [Zhejiang University], Jing Lv, Jian-Wei Zou and Tian-Xing Wu

See Applications / Water and Solvation.

- 1919–1928 **Determining equilibrium constants for dimerization reactions from molecular dynamics simulations,** Djurre H. De Jong, Lars V. Schäfer, Alex H. De Vries, Siewert J. Marrink, Herman J. C. Berendsen and Helmut Grubmüller [Max Planck Institute for Biophysical Chemistry]

With today's available computer power, free energy calculations from equilibrium molecular dynamics simulations “via counting” become feasible for an increasing number of reactions. We show that for simulation systems containing two molecules, the dimerization free energy is given by a formula of the form $\Delta G \propto \ln(P_1/P_0)$. Our theory is also applicable to high concentrations that typically have to be used in molecular dynamics simulations to keep the simulation system small, where the textbook dilute approximations fail.

- 1929–1943 **Impact of 2'-hydroxyl sampling on the conformational properties of RNA: Update of the CHARMM all-atom additive force field for RNA**, Elizabeth J. Denning, U. Deva Priyakumar, Lennart Nilsson and Alexander D. Mackerell Jr. [University of Maryland]

See Applications / Nucliec Acids.

- 1944–1951 **Web services as applications' integration tool: QikProp case study**, Abdel Laoui and Valery R. Polyakov [Aventis, 1041 Route 202-206 N]

Web services are a new technology that enables to integrate applications running on different platforms by using primarily XML to enable communication among different computers over the Internet. A generally applicable method of wrapping stand alone applications into Web services was developed and is described. To test the technology, it was applied to the QikProp for DOS (Windows).

- 1952–1961 **Design and parameterization of a stochastic cellular automaton describing a chemical reaction**, Pieter Van der Weeën[Ghent University], Jan M. Baetens and Bernard De Baets

Although most of the work concerned with reaction kinetics concentrates on empirical findings, stochastic models, and differential equations, a growing number of researchers is exploring other methods to elucidate reaction kinetics. In this work, the parameterization of an utter discrete spatio-temporal model, more specifically, a cellular automaton (CA), describing the reaction of HCl with CaCO₃, is suggested.

- 1962–1970 **Role of stereoelectronic features of imine and enamine in (S)-proline catalyzed mannich reaction of acetaldehyde: An in silico study**, Manjaly J. Ajitha and Cherumuttathu H. Suresh [National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum]

A detailed mechanistic investigation of sixteen possible diastereomeric pathways for the C-C bond formation step in (S)-proline catalyzed Mannich reaction of acetaldehyde with N-acetyl protected benzaldimine in acetonitrile solvent has been carried out to understand how stereoelectronic features invoke enantioselectivity of the final product.

- 1971–1981 **Assessment of TD-DFT- and TD-HF-based approaches for the prediction of exciton coupling parameters, potential energy curves, and electronic characters of electronically excited aggregates**, Wenlan Liu, Volker Settels, Philipp H. P. Harbach, Andreas Dreuw, Reinhold F. Fink and Bernd Engels [University of Würzburg]

The reliability of linear response approaches such as time-dependent Hartree–Fock (TD-HF) and time-dependent density functional theory (TD-DFT) for the prediction of the excited state properties of 3,4,9,10-tetracarboxylic-perylene-bisimide (PBI) aggregates is investigated.

- 1982–1992 **Multigrid solver for the reference interaction site model of molecular liquids theory**, Volodymyr P. Sergiievskiy, Wolfgang Hackbusch and Maxim V. Fedorov [Max Planck Institute of Mathematics in the Sciences]

In this article, we propose a new multigrid-based algorithm for solving integral equations of the reference interactions site model (RISM). We also investigate the relationship between the parameters of the algorithm and the numerical accuracy of the hydration free energy calculations by RISM.

- 1993–1997 **How reliable are GIAO calculations of ^1H and ^{13}C NMR chemical shifts? A statistical analysis and empirical corrections at DFT (PBE/3z) level**, Evgeniy Yu. Pankratyev [Institute of Organic Chemistry of Ufa Scientific Centre of Russian Academy of Sciences], Artur R. Tulyabaev and Leonard M. Khalilov

Reliability of calculated ^1H and ^{13}C NMR chemical shifts for various classes of organic compounds obtained with gauge-invariant atomic orbital (GIAO) approach has been studied at the PBE/3 ζ level (as implemented in PRIRODA code) using linear regression analysis with experimental data.

- 1998–2004 **Exchange coupling constants using density functional theory: Long-range corrected functionals**, Eliseo Ruiz [Universitat de Barcelona]

The presence of the self-interaction error in common exchange correlation functionals is one of the main drawbacks of calculations using methods based on Density Functional Theory. The recently developed asymptotically corrected functionals are an alternative way to solve the erroneous asymptotic behavior that may be at the origin of this error. Some of these functionals have been tested in the calculation of the exchange coupling constants of a number of transition metal dinuclear complexes.

- 2005–2011 **Alkali metal atom-aromatic ring: A novel interaction mode realizes large first hyperpolarizabilities of M@AR ($\text{M} = \text{Li}, \text{Na}, \text{and K}$, $\text{AR} = \text{pyrrole, indole, thiophene, and benzene}$)**, Guangtao Yu, Xu-Ri Huang, Wei Chen [Jilin University] and Chia-Chung Sun

Several new electride compounds M@pyrrole ($\text{M} = \text{Li}, \text{Na}, \text{and K}$), Li@AR ($\text{AR} = \text{indole, thiophene, and benzene}$), Li@tryptophan and Li@serotonin were designed and investigated, which exhibit considerably large first hyperpolarizabilities (β_0) (6705, 1116, 11399, 5781, 4808, 1536, 8106, and 9389 au, respectively) by comparison with their corresponding sole molecules pyrrole ($\beta_0 = 30$ au), indole (104 au), thiophene (6 au), benzene (0 au), tryptophan (159 au) and serotonin (151 au), respectively.

- 2012–2021 **Evolution of lone pair of excess electrons inside molecular cages with the deformation of the cage in $\text{e}_2@\text{C}_{60}\text{F}_{60}$ systems**, Yin-Feng Wang, Wei Chen, Guang-Tao Yu, Zhi-Ru Li [Institute of Theoretical Chemistry Jilin University], Di Wu and Chia-Chung Sun

For unusual $\text{e}_2@\text{C}_{60}\text{F}_{60}$ (I_h , D_{6h} , and D_{5d}) cage structures with two excess electrons, it is reported that not only the lone pair in singlet state but also two single excess electrons in triplet state can be encapsulated inside the $\text{C}_{60}\text{F}_{60}$ cages to form single molecular solvated dielectrons. For these excess electron systems, the three ground state structures have large vertical electron detachment energies (VDEs (I) of 1.720–2.283 eV and VDEs (II) of 3.959–5.288 eV), which shows their stabilities and suggests that the large $\text{C}_{60}\text{F}_{60}$ cage is the efficient container of excess electrons.

- 2022–2030 **The effect of iron and copper impurities on the wettability of sphalerite (110) surface**, Darren J. Simpson [University of South Australia], Thomas Bredow, Anand P. Chandra, Giuseppe P. Cavallaro and Andrea R. Gerson

The effect of impurities in the zinc sulfide mineral sphalerite on surface wettability has been investigated theoretically to shed light on previously reported conflicting results on sphalerite flotation.

- 2031–2040 **Optimization of parameters for molecular dynamics simulation using smooth particle-mesh Ewald in GROMACS 4.5**, Mark J. Abraham and Jill E. Gready [Australian National University]

See Methodology / Potentials and Parameters.

Journal of Molecular Modeling, 17(5), May, 2011.

- 921-928 **Molecular modeling and QSAR studies of a set of indole and benzimidazole derivatives as H4 receptor antagonists**, Joao Paulo S. Fernandes [Universidade de São Paulo], Kerly Fernanda M. Pasqualoto, Elizabeth I. Ferreira and Carlos A. Brandt

See Applications / QSAR.

- 929-937 **Can the positive aromatic ring be as π -electron donor in π -halogen bond? A MP2 theoretical investigation on the unusual π -halogen bond interaction between three-membered ring BNN 3⁺ and X1X2 (X1, X2 = F, Cl, Br)**, Hai-tao Qi, Fu-de Ren [North University of China], Jing-lin Zhang and Jing-yu Wang

The unusual π -halogen bond interactions are investigated between (BNN)₃⁺ and X1X2 (X1, X2 = F, Cl, Br) employing MP2 at 6-311++G(2d) and aug-cc-pVDZ levels according to the “CP (counterpoise) corrected potential energy surface (PES)” method.

- 939-953 **Identification of hotspot regions of MurB oxidoreductase enzyme using homology modeling, molecular dynamics and molecular docking techniques**, Vivek Kumar, Parameswaran Saravanan, Akanksha Arvind and C. Gopi Mohan [National Institute of Pharmaceutical Education and Research, Punjab]

See Applications / Homology Modeling

- 955-959 **Structural change from doping the gold cluster**, Yiji Tang [Shanghai Jiao Tong University], Shu-guang Wang and Jia Li

Doping gold clusters with a transition metal (M@Au_n) causes structural change. To determine the mechanism by which these changes occur, the central gold atom of Au₅ was doped with its same row transition metals Pt, Ir, Os, Re, and W. Based on theoretical calculations, a similar trend was found in other gold clusters.

- 961-970 **Phenylisoserine in the gas-phase and water: Ab initio studies on neutral and zwitterion conformers**, Joanna E. Rode, Jan Cz. Dobrowolski [Industrial Chemistry Research Institute, 8 Rydygiera Street] and Joanna Sadlej

The conformational landscape of phenylisoserine (PhIS) was studied. Trial structures were generated by allowing for all combinations of single-bond rotamers. Based on the B3LYP/aug-cc-pVDZ calculations 54 conformers were found to be stable in the gas phase.

- 971-978 **Molecular modeling and dynamics simulation of a histidine-tagged cytochrome b5**, Ying-Wu Lin [University of South China], Tian-Lei Ying and Li-Fu Liao

See Applications / Protein Dynamics.

- 979-985 **Computational molecular characterization of the flavonoid Morin and its Pt(II), Pd(II) and Zn(II) complexes**, Sergio A. Payán-Gómez, Norma Flores-Holguín, Antonino Pérez-Hernández, Manuel Piñón-Miramontes and Daniel Glossman-Mitnik [CIMAV]

In this work, we make use of a model chemistry within density functional theory (DFT) recently presented, which is called M05-2X, to calculate the molecular structure of the flavonoid Morin and its Pt(II), Pd(II) and Zn(II) complexes, as well to predict their IR and UV-Vis spectra, the dipole moment and polarizability, the free energy of solvation in different solvents as an indication of solubility, the HOMO and LUMO orbitals, and the chemical reactivity parameters that arise from Conceptual DFT. The calculated values are compared with the available experimental data for these molecules.

- 987-995 **Homology model and potential virus-capsid binding site of a putative HEV receptor Grp78**, Hai Yu, Shaowei Li [Xiamen University], Chunyan Yang, Minxi Wei and Cuiling Song, et al.

See Applications / Homology Modeling.

- 997-1006 **Electronic and molecular structure of M-DNA fragments**, Yury V. Rubin [NAS Ukraine], Leonid F. Belous and Anatolij A. Yakuba

See Applications / Nucliec Acids.

- 1007-1016 **Search for structures, potential energy surfaces, and stabilities of planar B_nP (n=1~7)**, Rongwei Shi, Jingling Shao, Cheng Wang, Xiaolei Zhu [Nanjing University of Technology] and Xiaohua Lu

We have systematically explored and investigated the geometrical structures, stability, growth pattern, bonding character, and potential energy surface (PES) of the possible isomers of each cluster for planar B_nP (n=1~7) at the CCSD(T)/6-311+;G(d)//B3LYP/6-311+G(d) level.

- 1017-1027 **Nitrosation of malononitrile by HONO, ClNO and N₂O₃: A theoretical study**, Kun Yang, Xiao-Fang Chen, Jian-Yong Liu [Chinese Academy of Sciences], Wei-Peng Lai and Bo-Zhou Wang

Nitrosation reactions of malononitrile by three nitrosating agents, HONO, ClNO, and N₂O₃, have been theoretically investigated at the B3LYP/cc-pVTZ and MP2/cc-pVDZ levels.

- 1029-1034 **Aqueous solubility of a simple (single-carbon) organic molecule as a function of its size & dipole moment**, Kamal I. Al-Malah [University of Hail]

The aqueous solubility of a single-carbon organic molecule as a function of its size & dipole moment was investigated. The molecular dipole moment was chosen to represent the polar character of a poly-atomic molecule.

- 1035-1040 **A DFT study of addition reaction between fragment ion (CH₂) units and fullerene (C₆₀) molecule**, Irineo Pedro Zaragoza, Jaime Vergara, Liliana Pérez-Manriquez and Roberto Salcedo [Universidad Nacional Autónoma de México]

The theoretical study of the interaction between CH₂ and fullerene (C₆₀) suggests the existence of an addition reaction mechanism; this feature is studied by applying an analysis of electronic properties.

- 1041-1049 **Exploration of the origin of large first hyperpolarizabilities of trisaza-bridged (36) fullerooids**, Lizhi Jiang, Jingyang Gu and Xiaolei Zhu [Nanjing University of Technology]

We investigate theoretically the structures and second-order nonlinear optical (NLO) responses (first hyperpolarizabilities) of 15 trisaza-bridged (36) fullerooids (series-A) and 15 triborane-bridged (36) fullerooids (series-B). 3A has smaller transition energy and smaller ground state dipole moment, resulting in relatively larger static first hyperpolarizability (10647 au).

- 1051-1060 **Study of ring influence and electronic response to proton transfer reactions. Reaction electronic flux analysis**, Barbara Herrera [Pontificia Universidad Católica de Chile]

In this article, a theoretical study of 1–5 proton transfers is presented. Two model systems which represent 1–5 proton transfer, 3-hidroxy-2-propenimine and salicylidenaniline have been studied.

- 1061-1068 **Nucleation and mobility model of Ag_n clusters adsorbed on perfect and oxygen vacancy MgO surfaces**, Yongfei Liu, Yan Wang [Beijing Normal University] and Guangju Chen

The structures and energy properties for Ag_n ($n = 1-8$) metal clusters adsorbed on the perfect and oxygen vacancy MgO surfaces have been studied by using the DFT/UB3LYP method with an embedded cluster model.

- 1069-1073 **Structures of Au/Pt bimetallic clusters: homogeneous or segregated?**, Fang Wang, Peng Liu and Dongju Zhang [Shandong University]

The question whether Au can alloy with Pt at the nano-scale size is still controversial. By performing density functional theory calculations for several small Au/Pt bimetallic clusters Au_mPt_n ($m + n = 4-6, 13$), we find that, in all the most stable geometries, Pt atoms prefer to assemble together to form the core while Au atoms like to surround the Pt atoms to form the shell, and that evenly mixed clusters are structurally unstable.

- 1075-1080 **Theoretical investigation of ZnO and its doping clusters**, Chunlei Wang, Shuhong Xu, Lihua Ye, Wei Lei and Yiping Cui [Southeast University]

Four clusters of ZnO, O–Zn–SR (–SR = ligand) and doping ZnO structures (with Cr, Cu, Al atoms) were investigated using density functional theory at the B3LYP/Lan2dz level.

- 1081-1090 **ATP and its N6-substituted analogues: parameterization, molecular dynamics simulation and conformational analysis**, Paweł Gruszczyński [University of Gdańsk], Krzysztof Smalara, Michał Obuchowski and Rajmund Kaźmierkiewicz

See Applications / Protein Dynamics.

- 1091-1108 **DFT modeling on the suitable crown ether architecture for complexation with Cs⁺ and Sr²⁺ metal ions**, Anil Boda, Sk. Musharaf Ali [Bhabha Atomic Research center], Madhav R. K. Shenoi, Hanmanth Rao and Sandip K. Ghosh

Crown ether architectures were explored for the inclusion of Cs⁺ and Sr²⁺ ions within nano-cavity of macrocyclic crown ethers using density functional theory (DFT) modeling.

- 1109-1119 **Study of interactions between Mycobacterium tuberculosis proteins: SigK and anti-SigK**, Vasavi Malkhed [Nizam College, Osmania University], Bargavi Gudlur, Bhargavi Kondagari, Ramasree Dulapalli and Uma Vuruputuri

See Applications / Ligand Binding.

- 1121-1131 **A tricotage-like failure of nanographene**, Elena F. Sheka [Peoples' Friendship University of Russia], Nadezhda A. Popova, Vera A. Popova, Ekaterina A. Nikitina and Landysh H. Shaymardanova

The response of a nanographene sheet to external stresses was considered in terms of a mechanochemical reaction. The quantum chemical realization of the approach was based on the coordinate-of-reaction concept for the purpose of introducing a mechanochemical internal coordinate (MIC) that specifies a deformational mode.

- 1133-1139 **First principles calculations of the electronic and chemical properties of graphene, graphane, and graphene oxide**, J. J. Hernández Rosas, R. E. Ramírez Gutiérrez, A. Escobedo-Morales and Ernesto Chigo Anota [Benemérita Universidad Autónoma de Puebla]

The electrical and chemical properties of graphene ($C_{24}H_{12}$), graphane ($C_{24}H_{24}$) and graphene oxide ($C_{54}H_{17}O_3(OH)_3COOH$) were studied through the density functional theory (DFT) at level of Local Density Approximation (LDA) using a model C_nH_m like.

- 1141-1147 **Molecular dynamics simulation of drug uptake by polymer**, M. Subashini, Padma V. Devarajan, Ganeshchandra S. Sonavane and Mukesh Doble [IIT-Madras]

See Applications / Medicinal Chemistry and Drug Design.

- 1149-1161 **Docking and 3D-QSAR modeling of cyclin-dependent kinase 5/p25 inhibitors**, Zaheer Ul Haq [University of Karachi], Reaz Uddin, Lam Kok Wai, Abdul Wadood and Nordin Haji Lajis

See Applications / QSAR.

- 1163-1172 **Modeling the adsorptive selectivity of carbon nanotubes for effective separation of CO₂/N₂ mixtures**, Seyedeh Saleheh Razavi, Seyed Majid Hashemianzadeh [Iran University of Science and Technology] and Hedayat Karimi

Canonical Monte Carlo (CMC) simulations were carried out to investigate the behavior of CO₂ and N₂ mixtures upon adsorption on single walled carbon nanotubes (CNTs).

- 1173-1182 **Structure-based in-silico rational design of a selective peptide inhibitor for thymidine monophosphate kinase of mycobacterium tuberculosis**, Manoj Kumar, Sujata Sharma, Alagiri Srinivasan, Tej P. Singh and Punit Kaur [All India Institute of Medical Sciences]

Tuberculosis still remains one of the most deadly infectious diseases. The emergence of drug resistant strains has fuelled the quest for novel drugs and drug targets for its successful treatment. Based on a detailed evaluation of known inhibitors and available three-dimensional structures of TMPK, several peptidic inhibitors were designed. In silico docking and selectivity analysis of these inhibitors with TMPK from M.tb and human was carried out to examine their differential binding at the active site.

- 1183-1189 **Molecular dynamics simulations of the minor ampullate spidroin modular amino acid sequence from *Parawixia bistriatra*: insights into silk tertiary structure and fibre formation**, André M. Murad and Elíbio L. Rech [Parque Estação Biológica – PqEB]

See Applications / Protein Dynamics.

- 1191-1205 **3D-QSAR and molecular docking studies of azaindole derivatives as Aurora B kinase inhibitors**, Ping Lan, Wan-Na Chen, Ping-Hua Sun and Wei-Min Chen [Jinan University]

See Applications / Medicinal Chemistry and Drug Design.

- 1207-1221 **Exploring the structure of opioid receptors with homology modeling based on single and multiple templates and subsequent docking: A comparative study**, Indrani Bera, Aparna Laskar and Nanda Ghoshal [Indian Institute of Chemical Biology, Kolkata]

See Methodology / Homology Modeling.

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1 APPLICATIONS (89)

Page 2

1.1 Small Molecules (19)

Water and Solvation	Page 2	Zeolites	Page 6
Organic Solvents	Page 3	Carbon Nanoparticles	Page 6
Med. Chem. And Drug Design	Page 3	Crystal Growth	Page 7
QSAR	Page 5		

1.2 Biopolymers (70)

Bioinformatics and Cheminformatics	Page 8	Ligand Binding	Page 16
Protein Secondary Structure	Page 9	Enzyme Catalysis	Page 18
Protein Structure Prediction	Page 9	Protein-Protein Interactions	Page 21
Comparative or Homology Modeling	Page 10	Membrane Proteins	Page 21
Protein Conformational Analysis	Page 11	Protein Folding	Page 24
Protein Dynamics	Page 12	Protein-Nucleic Acids	Page 25
Free Energy Calculations	Page 14	Nucleic Acids	Page 26

1.3 Polymers

1.4 Surfaces, Catalysts and Material

Page 27

2 METHODOLOGY (27)

Page 28

QSAR	Page 28	Free energy Perturbations	Page 31
Potentials and Parameters	Page 28	QM & QM/MM	Page 32
Solvation Energy	Page 29	Comparative or Homology	Page 33
Molecular Dynamics	Page 30	Ligand Docking	Page 33

3 JOURNAL REVIEWS (4)

Page 36

Journal of Molecular Graphics and Modeling, 29 (8), August, 2011.
 Journal of Computational Chemistry, 32 (10), July, 2011.
 Journal of Computational Chemistry, 32 (11), August, 2011.
 Journal of Molecular Modeling, 17 (6), June, 2011.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 48

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

New Theoretical Method for Rapid Prediction of Solvation Free Energy in Water

Shuangliang Zhao, Zhehui Jin, and Jianzhong Wu [University of California, Riverside]

J. Phys. Chem. B., **115**, 6971–6975, 2011.

We present a new theoretical method for rapid calculation of the solvation free energy in water by combining molecular simulation and the classical density functional theory (DFT). The DFT calculation is based on an accurate free-energy functional for water that incorporates the simulation results for long-range correlations and the fundamental measure theory for the molecular excluded-volume effects. Because simulation is applied only to the particular thermodynamic condition of interest, the hybrid method is computationally much more efficient than conventional ways of solvation free energy calculations.

Disaccharide Topology Induces Slowdown in Local Water Dynamics

Ana Vila Verde and R. Kramer Campen [FOM Institute AMOLF]

J. Phys. Chem. B., **115**, 7069–7084, 2011.

Molecular level insight into water structure and structural dynamics near proteins, lipids, and nucleic acids is critical to the quantitative understanding of many biophysical processes. Unfortunately, understanding hydration and hydration dynamics around such large molecules is challenging because of the necessity of deconvoluting the effects of topography and chemical heterogeneity. Here we study, via classical all-atom simulation, the water structure and structural dynamics around two biologically relevant solutes large enough to have significant chemical and topological heterogeneity but small enough to be computationally tractable: the disaccharides kojibiose and trehalose.



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Dr. David Busath edited volumes 7-14

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Organic Solvents

Docking glycosaminoglycans to proteins: analysis of solvent inclusion

Sergey A. Samsonov [BIOTEC TU Dresden], Joan Teyra and M. Teresa Pisabarro

J. Comp. Aided Mol. Des. **25**, 477-489, 2011.

Glycosaminoglycans (GAGs) are anionic polysaccharides, which participate in key processes in the extracellular matrix by interactions with protein targets. Due to their charged nature, accurate consideration of electrostatic and water-mediated interactions is indispensable for understanding GAGs binding properties. However, solvent is often overlooked in molecular recognition studies. Here we analyze the abundance of solvent in GAG-protein interfaces and investigate the challenges of adding explicit solvent in GAG-protein docking experiments. We observe PDB GAG-protein interfaces being significantly more hydrated than protein-protein interfaces.

Methanol Strengthens Hydrogen Bonds and Weakens Hydrophobic Interactions in Proteins – A Combined Molecular Dynamics and NMR study

Soyoun Hwang, Qiang Shao, Howard Williams, Christian Hilty, and Yi Qin Gao [Peking University]

J. Phys. Chem. B., **115**, 6653–6660, 2011.

A combined simulation and experimental study was performed to investigate how methanol affects the structure of a model peptide BBA5. BBA5 forms a stable β -hairpin- α -helix structure in aqueous solutions. Molecular dynamics simulations were performed in water and methanol/water solutions using all-atom explicit models. NMR experiments were used to test the calculated results. The combined theoretical and experimental studies suggest that methanol strengthens the interactions between the polar backbone of the peptide and thus enhances the secondary structure formation; at the same time methanol weakens the hydrophobic interactions and results in an expansion of the hydrophobic core and an increase in gyration.

Medicinal Chemistry and Drug Design

Docking and SAR studies of D- and L-isofagomine isomers as human β -glucocerebrosidase inhibitors

Atsushi Kato [University of Toyama], Saori Miyauchi, Noriko Kato, Robert J. Nash, Yuichi Yoshimura, Izumi Nakagome, Shuichi Hirono, Hiroki Takahata, Isao Adachi

Bioorg. and Med.Chem., **19**, 3558-3568, 2011.

We report the structure–activity relationship of a series of d-, and l-isofagomine and fagomine isomers as glycosidase inhibitors. Our study revealed that a positive charge at the anomeric position of d-isofagomines enhanced the potency toward β -glycosidases, while the epimerization at the C3 OH group drastically reduced their inhibitory potency by over three orders of magnitude. Furthermore, d-3,4-di-epi-isofagomine abolished their inhibition activities against all enzymes. l-Isfagomine was also a fairly potent inhibitor of human β -glucocerebrosidase, with an IC_{50} value of 8.7 μ M.

Medicinal Chemistry and Drug Design (Cont'd)

Design, synthesis and molecular docking studies of novel triazole as antifungal agent

Xiaoyun Chai, Jun Zhang, Yongbing Cao, Yan Zou, Qiuye Wu, Dazhi Zhang, Yuanying Jiang, Qingyan Sun [Second Military Medical University]

Europ. Jou. Med. Chem., **46**, 3167-3176, 2011.

In order to meet the urgent need for novel antifungal agents with improved activity and broader spectrum, a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols were designed, synthesized and evaluated as antifungal agents. The MIC₈₀ values indicate that the compounds **7a–7q**, **8a–8d** showed higher antifungal activities against *Candida albicans* than **5a–5i**, **6a–6j**.

A class of oral N-[(1S,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carbonyl]-N'-(amino-acid-acyl)hydrazine: Discovery, synthesis, in vitro anti-platelet aggregation/in vivo anti-thrombotic evaluation and 3D QSAR analysis

Kun Yao, Ming Zhao, Xiaoyi Zhang, Yuji Wang, Li Li, Meiqing Zheng, Shiqi Peng [Capital Medical University]

Europ. Jou. Med. Chem., **46**, 3237-3249, 2011.

The in vivo anti-thrombotic activities of amino acid modified tetrahydro-β-carbolines depended upon the proximity of the side chain of the amino acid residue to the carboline-cycle. Based on this proximity the computerized screening of various tetrahydro-β-carboline derivatives was performed and N-[(1S,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carbonyl]-N'-(amino-acid-acyl)hydrazines were explored having large proximity. The in vivo anti-thrombotic assays explored that at a dose of 10 nmol/kg eighteen novel N-[(1S,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carbonyl]-N'-(amino-acid-acyl)hydrazines were orally efficacious.

Ligand-based discovery of novel trypanosomicidal drug-like compounds: In silico identification and experimental support

Juan Alberto Castillo-Garit [Central University of Las Villas], Maria Celeste Vega, Miriam Rolón, Yovani Marrero-Ponce, Alicia Gómez-Barrio, José A. Escario, Alfredo Alvarez Bello, Alina Montero, Francisco Torrents, Facundo Pérez-Giménez, Vicente J. Arán, Concepción Abad

Europ. Jou. Med. Chem., **46**, 3324-3330, 2011.

Two-dimensional bond-based linear indices and linear discriminant analysis are used in this report to perform a quantitative structure–activity relationship study to identify new trypanosomicidal compounds. A database with 143 anti-trypanosomal and 297 compounds having other clinical uses, are utilized to develop the theoretical models. The best discriminant models computed using bond-based linear indices provides accuracies greater than 90 for both training and test sets. Our models identify as anti-trypanosomals five out of nine compounds of a set of already-synthesized substances.

A class of Trp-Trp-AA-OBzl: Synthesis, in vitro anti-proliferation/in vivo anti-tumor evaluation, intercalation-mechanism investigation and 3D QSAR analysis

Xiaoyi Zhang, Yifan Yang, Ming Zhao, Liu Liu, Meiqing Zheng, Yuji Wang, Jianhui Wu, Shiqi Peng [Capital Medical University]

Europ. Jou. Med. Chem., **46**, 2736-2747, 2011.

From the anti-tumor active N-tryptophanyl-β-carboline-3-carboxylic acid benzyl ester and β-carboline-3-carbonyltryptophan benzyl ester, a pharmacophore, Trp-Trp-OBzl, was drawn. Based on the DOCK scores amino acid residue was inserted into the C-terminus of Trp-Trp-OBzl and twenty Trp-Trp-AA-OBzls (AA = amino acid residues) were provided as DNA intercalators. On the in vitro and in vivo models seventeen Trp-Trp-AA-OBzls were anti-tumor active, and twelve Trp-Trp-AA-OBzls were more active than cytarabine.

Medicinal Chemistry and Drug Design (Cont'd)

SHAFTS: A Hybrid Approach for 3D Molecular Similarity Calculation. 2. Prospective Case Study in the Discovery of Diverse p90 Ribosomal S6 Protein Kinase 2 Inhibitors To Suppress Cell Migration

Weiqiang Lu, Xiaofeng Liu, Xianwen Cao, Mengzhu Xue, Kangdong Liu, Zhenjiang Zhao, Xu Shen, Hualiang Jiang, Yufang Xu, Jin Huang, and Honglin Li [East China University of Science and Technology]

J. Med. Chem. **54**, 3564–3574, 2011.

We described a prospective application of ligand-based virtual screening program SHAFTS to discover novel inhibitors for p90 ribosomal S6 protein kinase 2 (RSK2). Taking the putative 3D conformations of two weakly binding RSK2 NTKD inhibitors as query templates, SHAFTS was used to perform 3D similarity based virtual screening because of a lack of crystal structure of RSK2 protein, thus leading to the identification of several novel scaffolds that would have been missed by conventional 2D fingerprint methods. The most potent hit compounds show low micromolar inhibitory activities against RSK2. In particular, one of the hit compounds exhibits potent antimigration activity against the MDA-MB-231 tumor cell.

Rational questing for potential novel inhibitors of FabK from *Streptococcus pneumoniae* by combining FMO calculation, CoMFA 3D-QSAR modeling and virtual screening

Qingye Zhang, Chan Yu, Jun Min, Ziniu Yu [Huazhong Agricultural University], Yan Wang and Jin He, et al.

J. Mol. Mod., **17**, 1483-1492, 2011.

Enoyl-acyl carrier protein (ACP) reductase (ENR) is an attractive and potential target for developing selective antibacterial agents. Recent studies showed that FabK is the sole isoform of ENR in *Streptococcus pneumoniae*, and at the same time an X-ray crystallographic study of FabK from *S. pneumoniae* (SpFabK) was reported for the first time. Based on above information, the interaction mechanism and pair interaction energies between ligand and the active site of SpFabK were analyzed with the ab initio fragment molecular orbital (FMO) calculation based on the FlexX docking model at the FMO-RHF/6-31G* level.

Quantitative Structure-Activity Relations

Singular value decomposition analysis of the torsional angles of dopamine reuptake inhibitor GBR 12909 analogs: effect of force field and charges

Deepangi Pandit, Anna Fiorentino, Supreet Bindra and Carol A. Venanzi [New Jersey Institute of Technology]

J. Mol. Mod., **17**, 1343-1351, 2011.

Three-dimensional quantitative structure-activity relationship (3D-QSAR) analysis of large, flexible molecules, such as the dopamine reuptake inhibitor GBR 12909 (1), is complicated by the fact that they can take on a wide range of closely-related conformations. The first step in the analysis is to classify the conformers into groups. Over 600 conformers each of a piperazine (2) and piperidine (3) analog of 1 were generated by random search conformational analysis using the Merck Molecular Force Field (MMFF94). Singular value decomposition (SVD) was used to group the conformers of 2 and 3 by the similarity of their non-ring torsional angles.

Zeolites

A New Aluminosilicate Molecular Sieve with a System of Pores between Those of ZSM-5 and Beta Zeolite

Manuel Moliner, Jorge Gonzalez, M. Teresa Portilla, Tom Willhammar, Fernando Rey, Francisco J. Llopi, Xiaodong Zou, and Avelino Corma [Universidad Politecnica de Valencia]

J. Am. Chem. Soc., **133**, 9497–9505, 2011.

A new aluminosilicate zeolite (ITQ-39) has been synthesized. This is an extensively faulted structure with very small domains that makes the structure elucidation very difficult. However, a combination of adsorption spectroscopy and reactivity studies with selected probe molecules suggests that the pore structure of ITQ-39 is related to that of Beta zeolite, with a three-directional channel system with large pores (12-MR), but with an effective pore diameter between those of Beta and ZSM-5, or a three-directional channel system with interconnected large (12-MR) and medium pores (10-MR).

Selection and Validation of Charge and Lennard-Jones Parameters for QM/MM Simulations of Hydrocarbon Interactions with Zeolites

Paul M. Zimmerman, Martin Head-Gordon [University of California], and Alexis T. Bell

J. Chem. Theor. and Comp, **7**, 1695–1703, 2011.

Quantum mechanics/molecular mechanics (QM/MM) models are an appealing method for performing zeolite simulations. In QM/MM, a small cluster chosen to encompass the active center is described by QM, while the rest of the zeolite is described by MM. In the present study, we demonstrate that the charges and Lennard-Jones parameters on Si and O must be chosen properly for QM/MM calculations of adsorption energies and activation energies to agree closely with full QM calculations. The selection of parameters for Si and O is based on using the ω B97X-D functional for DFT calculations of the QM region, which is effective in capturing the effects of van der Waals interactions.

Carbon Nanoparticles

Carbon Nanotube Sidewall Functionalization with Carbonyl Compounds—Modified Birch Conditions vs the Organometallic Reduction Approach

Benjamin Gebhardt, Zois Syrgiannis, Claudia Backes, Ralf Graupner, Frank Hauke, and Andreas Hirsch [University of Erlangen-Nuremberg]

J. Am. Chem. Soc., **133**, 7985–7995, 2011.

Covalent addition reactions turned out to be one of the most important functionalization techniques for a structural alteration of single walled carbon nanotube (SWCNT) scaffolds. We present a significant modification of the reductive alkylation/arylation sequence, the so-called Billups reaction, which extends the portfolio of electrophiles for covalent sidewall functionalization to carbonyl compounds—ketones, esters, and even carboxylic acid chlorides. Moreover, these carbonyl-based electrophiles can also be used as secondary functionalization reagents for anionic SWCNT intermediates, derived from a primary nucleophilic addition step.

Carbon Nanoparticles (Cont'd)

On the applicability of cluster models to study the chemical reactivity of carbon nanotubes

Pablo A. Denis [Facultad de Química] and Federico Iribarne

J. Comp. Chem. **32**, 2397–2403, 2011.

We have performed a comparative study on the reactivity of metallic and semiconducting nanotubes using infinite and finite models. Infinite models were created using periodic boundary conditions while finite ones were constructed by means of hydrogen terminated nanotubes sections. Cluster models systematically underestimate the reactivity of metallic single wall carbon nanotube (SWCNT)s. We have confirmed that metallic nanotubes are more reactive than semiconducting species, in disagreement with previous works.

Computational modeling of a rotary nanopump

A. Lohrasebi [University of Isfahan], Y. Jamali

J. Mol.Graph. and Mod., **29**, 1025-1029, 2011.

The dynamics of a rotary nanopump, consisting of three coaxial carbon nanotubes and a number of graphene blades, has been simulated via application of the molecular dynamics (MD) method. In this nanopump the inner nanotube, the middle carbon nanotube with together the graphene blades and the outer nanotube are used as the shaft, rotor, and sleeve of the pump, respectively. The rotary motion of the rotor is due to the mechanical rotation of the two first carbon rings of the rotor's carbon nanotube. We found that this pump flow the gas atoms between two sides of the nanopump and it can produce an atomic gradient.

Very-high-strength (60-GPa) carbon nanotube fiber design based on molecular dynamics simulations

Charles F. Cornwell [U.S. Army Engineer Research and Development Center] and Charles R. Welch

Jou. Chem. Phys., **134**, 204708, 2011.

The mechanical properties of carbon nanotubes such as low density, high stiffness, and exceptional strength make them ideal candidates for reinforcement material in a wide range of high-performance composites. Molecular dynamics simulations are used to predict the tensile response of fibers composed of aligned carbon nanotubes with intermolecular bonds of interstitial carbon atoms. The effects of bond density and carbon nanotube length distribution on fiber strength and stiffness are investigated.

Crystal Growth

A second Ig-like domain identified in dystroglycan by molecular modelling and dynamics

Maria Cristina De Rosa, Davide Pirolli, Manuela Bozzi, Francesca Sciandra, Bruno Giardina, Andrea Brancaccio [Università Cattolica del Sacro Cuore]

J. Mol.Graph. and Mod., **29**, 1015-1024, 2011.

Dystroglycan (DG) is a cell surface receptor which is composed of two subunits that interact noncovalently, namely α - and β -DG. In skeletal muscle, DG is the central component of the dystrophin–glycoprotein complex (DGC) that anchors the actin cytoskeleton to the extracellular matrix. To date only the three-dimensional structure of the N-terminal region of α -DG has been solved by X-ray crystallography. To expand such a structural analysis, a theoretical molecular model of the murine α -DG C-terminal region was built based on folding recognition/threading techniques.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Fast docking using the CHARMM force field with EADock DSS

Aurélien Grosdidier, Vincent Zoete and Olivier Michielin
[Swiss Institute of Bioinformatics]

J. Comp. Chem. **32**, 2149–2159, 2011.

The prediction of binding modes (BMs) occurring between a small molecule and a target protein of biological interest has become of great importance for drug development. EADock2 is an docking software. Its multiobjective scoring function was designed around the CHARMM22 force field and the FACTS solvation model. However, the major drawback of such a software design lies in its computational cost. EADock dihedral space sampling (DSS) is built on the most efficient features of EADock2, namely its hybrid sampling engine and multiobjective scoring function. Its performance is equivalent to that of EADock2 for drug-like ligands, while the CPU time required has been reduced by several orders of magnitude.

Integrating computational and mixture-based screening of combinatorial libraries

Austin B. Yongye, Clemencia Pinilla, Karina Martínez-Mayorga [Torrey Pines Institute for Molecular Studies], Jose L. Medina-Franco, Marc A. Giulianotti and Colette T. Dooley, et al.

J. Mol.Mod., **17**, 1473-1482, 2011.

Mixture-based synthetic combinatorial library (MB-SCL) screening is a well-established experimental approach for rapidly retrieving structure–activity relationships (SAR) and identifying hits. Virtual screening is also a powerful approach that is increasingly being used in drug discovery programs and has a growing number of successful applications. However, limited efforts have been made to integrate both techniques. To this end, we combined experimental data from a MB-SCL of bicyclic guanidines screened against the κ -opioid receptor and molecular similarity methods.

CafeMol: A Coarse-Grained Biomolecular Simulator for Simulating Proteins at Work

Hiroo Kenzaki, Nobuyasu Koga, Naoto Hori, Ryo Kanada, Wenfei Li, Kei-ichi Okazaki, Xin-Qiu Yao, and Shoji Takada [Kyoto University]

J. Chem. Theor. and Comp, **7**, 1979–1989, 2011.

For simulating proteins at work in millisecond time scale or longer, we develop a coarse-grained (CG) molecular dynamics (MD) method and software, CafeMol. At the resolution of one-particle-per-residue, CafeMol equips four structure-based protein models: (1) the off-lattice Go model, (2) the atomic interaction based CG model for native state and folding dynamics, (3) the multiple-basin model for conformational change dynamics, and (4) the elastic network model for quasiharmonic fluctuations around the native structure. Ligands can be treated either explicitly or implicitly.

Bioinformatics and Cheminformatics (Cont'd)

Identification of novel inhibitors of mitogen-activated protein kinase phosphatase-1 with structure-based virtual screening

Hwangseo Park [Sejong University], Jeong-Yi Jeon, Song Yi Kim, Dae Gwin Jeong and Seong Eon Ryu

J. Comp. Aided Mol. Des. **25**, 469-475, 2011.

Mitogen-activated protein kinase phosphatase-1 (MKP-1) has proved to be an attractive target for the development of therapeutics for the treatment of cancer. We report the first example for a successful application of the structure-based virtual screening to identify the novel inhibitors of MKP-1. It is shown that the efficiency of virtual screening can be enhanced significantly by the incorporation of a new solvation energy term in the scoring function. The newly found inhibitors have desirable physicochemical properties as a drug candidate and reveal a moderate potency with IC₅₀ values ranging from 20 to 50 μ M.

Protein Secondary Structure

Chiral Sum Frequency Generation Spectroscopy for Characterizing Protein Secondary Structures at Interfaces

Li Fu, Jian Liu, and Elsa C. Y. Yan [Yale University]

J. Am. Chem. Soc., **133**, 8094–8097, 2011.

In situ and real-time characterization of protein secondary structures at interfaces is important in biological and bioengineering sciences, yet remains technically challenging. In this study, we used chiral sum frequency generation (SFG) spectroscopy to establish a set of vibrational optical markers for characterizing protein secondary structures at interfaces. We discovered that the N–H stretches along the peptide backbones of α -helices can be detected in chiral SFG spectra. We further observed that the chiral vibrational signatures of the N–H stretch together with the peptide amide I are unique to α -helix, β -sheet, and random coil at interfaces.

Protein Structure Prediction

A PM6 study of Rhodopseudomonas Acidophila light harvesting center II B800 bacteriochlorophylls in representative protein environment

Sina Türeli [Boğaziçi University] and Tereza Varnali

J. Mol.Mod., **17**, 1273-1281, 2011.

Bacterial light-harvesting II (LH-II) centers contain two types of Bacteriochlorophylls (Bchl). One is named B800 and found as a single molecule within one monomer of the complex while the other named B850 is found as a dimer. Both types of molecules are attached to the protein chain via ligation of their central Magnesium atom to an either Histidine or Deoxymethionine amino acid. Both the ligation and the hydrogen bonding are thought to have an effect on electronic structure of the Bchl hence its UV absorbance and energy transfer rate.

Comparative or Homology Modeling

Computational protein design: engineering molecular diversity, nonnatural enzymes, nonbiological cofactor complexes, and membrane proteins

Jeffery G Saven [University of Pennsylvania]
Curr. Opin. Chem. Biol., **15**, 452-457, 2011.

Computational and theoretical methods are advancing protein design as a means to create and investigate proteins. Such efforts further our capacity to control, design and understand biomolecular structure, sequence and function. Herein, the focus is on some recent applications that involve using theoretical and computational methods to guide the design of protein sequence ensembles, new enzymes, proteins with novel cofactors, and membrane proteins.

Simulation on the structure of pig liver esterase

Daniel Hasenpusch, Uwe T. Bornscheuer and Walter Langel
[University of Greifswald]

J. Mol.Mod., **17**, 1493-1506, 2011.

A homology model for pig liver esterase was generated on the basis of human carboxyl esterase (hCE) and subjected to extensive molecular dynamics simulations. By virtual mutations the isoenzymes PLE1-6 and APLE were obtained, and the PLE1 trimer was built from the respective model of hCE. Stable structures for all systems were attained after simulations in solution for 12-18 ns, and contact zones between the monomers in the trimer are described. By evaluation of RMSD values of the residues in the monomer a rigid backplane with a number of β -strands and a flexible front part containing several α helices are distinguished.

Structural modeling and molecular dynamics simulation of the actin filament

Thomas Splettstoesser, Kenneth C. Holmes, Frank Noé and Jeremy C. Smith [University of Tennessee/ORNL]

Proteins: Stru. Fun. and Bioinfo. **79**, 2033–2043, 2011.

Actin is a major structural protein of the eukaryotic cytoskeleton and enables cell motility. Here, we present a model of the actin filament (F-actin) that not only incorporates the global structure of the recently published model by Oda et al. but also conserves internal stereochemistry. A comparison is made using molecular dynamics simulation of the model with other recent F-actin models. In addition, simulations of the model are carried out in states with both ADP or ATP bound and local hydrogen-bonding differences characterized.

Leukocyte integrin α L β 2 transmembrane association dynamics revealed by coarse-grained molecular dynamics simulations

Choon-Peng Chng [A*STAR Institute of High Performance Computing] and Suet-Mien Tan

Proteins: Stru. Fun. and Bioinfo. **79**, 2203–2213, 2011.

Integrins are transmembrane (TM) proteins that mediate bidirectional mechanical signaling between the extracellular matrix and the cellular cytoskeletal network. Each integrin molecule consists of non-covalently associated α - and β -subunits, with each subunit consisting of a large ectodomain, a single-pass TM helix, and a short cytoplasmic tail. Here, we compare the self-assembly dynamics of α L β 2 and α II β 3 TM helices in a model membrane using coarse-grained molecular dynamics simulations. We found that although α II β 3 TM helices associate more easily, packing is suboptimal. In contrast, α L β 2 TM helices achieve close-to-optimal packing.

Protein Confirmation Analysis

Hairpin conformation of an 11-mer peptide

Chong Geok Mei, Nicole Jahr, David Singer, Stefan Berger
[University Leipzig]

Bioorg. and Med.Chem., **19**, 3497-3501, 2011.

An 11-mer peptide taken from a subsequence of the human protein ubiquitin was synthesized. The peptide has been fully characterized by NMR spectroscopy using chemical shift analysis and by NOE measurements. The conformation was calculated using state of the art MD methods of protein chemistry. A hairpin conformation was found which is to a large part identical with the structure of this peptide fragment within the human ubiquitin.

Insights into the Dynamics of HIV-1 Protease: A Kinetic Network Model Constructed from Atomistic Simulations

Nan-jie Deng, Weihua Zheng, Emillio Gallicchio, and Ronald M. Levy [The State University of New Jersey]

J. Am. Chem. Soc., **133**, 9387–9394, 2011.

The conformational dynamics in the flaps of HIV-1 protease plays a crucial role in the mechanism of substrate binding. We develop a kinetic network model, constructed from detailed atomistic simulations, to determine the kinetic mechanisms of the conformational transitions in HIV-1 PR. To overcome the time scale limitation of conventional molecular dynamics (MD) simulations, our method combines replica exchange MD with transition path theory (TPT) to study the diversity and temperature dependence of the pathways connecting functionally important states of the protease.

Detailed Atomistic Analysis of the HIV-1 Protease Interface

Sergio Filipe Sousa, Bruno Tamames, Pedro Alexandrino Fernandes, and Maria Joao Ramos [Universidade do Porto]

J. Phys. Chem. B., **115**, 7045–7057, 2011.

HIV-1 protease is a very attractive target for the development of new anti-HIV drugs and has been extensively studied over the past decades. In this study, we present a detailed atomic level characterization of the dimer interface in the enzyme HIV-1 protease through computational alanine scanning mutagenesis and molecular dynamics simulations. The results presented illustrate the high energetic importance for dimer formation of a small set of five amino acid residue pairs at the subunit interface—Leu5, Ile50, Arg87, Leu97, and Phe99—and provide important clues on the most important structural and energetic determinants for dimer formation.

Molecular Conformations in the Pentasaccharide LNF-1 Derived from NMR Spectroscopy and Molecular Dynamics Simulations

Elin Sawen, Baltzar Stevansson, Jennie Ostervall, Arnold Maliniak, and Goran Widmalm [Stockholm University]

J. Phys. Chem. B., **115**, 7109–7121, 2011.

The conformational dynamics of the human milk oligosaccharide lacto-N-fucopentaose (LNF-1), α -l-Fucp-(1 $\rightarrow$ 2)- β -d-Galp-(1 $\rightarrow$ 3)- β -d-GlcpNAc-(1 $\rightarrow$ 3)- β -d-Galp-(1 $\rightarrow$ 4)-d-Glcp, has been analyzed using NMR spectroscopy and molecular dynamics (MD) computer simulations. Employing the Hadamard ^{13}C -excitation technique and the J-HMBC experiment, ^1H , ^{13}C transglycosidic J coupling constants were obtained, and from one- and two-dimensional ^1H , ^1H T-ROESY experiments, proton–proton cross-relaxation rates were determined in isotropic D_2O solution.

Protein Conformational Analysis (Cont'd)

Coarse-grained modeling of conformational transitions underlying the processive stepping of myosin V dimer along filamentous actin

Wenjun Zheng [University at Buffalo]

Proteins: Stru. Fun. and Bioinfo. **79**, 2291–2305, 2011.

To explore the structural basis of processive stepping of myosin V along filamentous actin, we have performed comprehensive modeling of its key conformational states and transitions with an unprecedented residue level of details. We have built structural models for a myosin V monomer complexed with filamentous actin at four biochemical states [adenosine diphosphate (ATP)-, adenosine diphosphate (ADP)-phosphate-, ADP-bound or nucleotide-free]. Then we have modeled a myosin V dimer (consisting of lead and rear head) at various two-head-bound states with nearly straight lever arms rotated by intramolecular strain.

Protein Dynamics

Molecular Dynamics Simulation of the Antiamoebin Ion Channel: Linking Structure and Conductance

Michael A. Wilson, Chenyu Wei, Pär Bjelkmar, B.A. Wallace, Andrew Pohorille [University of California, San Francisco]

Biophysical Journal. **100**, 2394-2402, 2011.

Molecular-dynamics simulations were carried out to ascertain which of the potential multimeric forms of the transmembrane peptaibol channel, antiamoebin, is consistent with its measured conductance. Estimates of the conductance obtained through counting ions that cross the channel and by solving the Nernst-Planck equation yield consistent results, indicating that the motion of ions inside the channel can be satisfactorily described as diffusive. On this basis, we propose that the antiamoebin channel consists of six monomers. Its pore is large enough to accommodate K^+ and Cl^- with their first solvation shells intact.

Protein-Binding Molecular Switches via Host–Guest Stabilized DNA Hairpins

D. Calvin Harris, Benjamin R. Saks, and Janarthanan Jayawickramarajah [Tulane University]

J. Am. Chem. Soc., **133**, 7676–7679, 2011.

Molecular switches, with target protein-binding activity controlled by prior binding to specific input stimuli, are ubiquitously used in Nature. However, the emulation of such responsive systems, especially in a de novo fashion, remains a significant challenge. Herein, we disclose a strategy that harnesses an intramolecular β -CD/adamantane host–guest interaction to generate a stabilized DNA hairpin ($\Delta T_m = 17^\circ C$) that undergoes an input oligonucleotide (ODN)-selective structural transformation from a stem-loop conformation to a duplex.

Monomer-Resolved Simulations of Cluster-Forming Dendrimers

Dominic A. Lenz, Bianca M. Mladek, Christos N. Likos, Gerhard Kahl, and Ronald Blaak [Heinrich-Heine-Universität Düsseldorf]

J. Phys. Chem. B., **115**, 7218–7226, 2011.

We present results of monomer-resolved Monte Carlo simulations for a system of amphiphilic dendrimers of the second generation. Our investigations validate a coarse-grained level description based on the zero-density limit effective pair-interactions for low and intermediate densities, which predicted the formation of stable, finite aggregates in the fluid phase. Indeed, we find that these systems form a homogeneous fluid for low densities, which, on increasing the density, spontaneously transforms into a fluid of clusters of dendrimers.

Protein Dynamics (Cont'd)

Inhibition of Aggregation of Amyloid Peptides by Beta-Sheet Breaker Peptides and Their Binding Affinity

Man Hoang Viet, Son Tung Ngo, Nguyen Sy Lam, and Mai Suan Li [Polish Academy of Sciences]

J. Phys. Chem. B., **115**, 7433–7446, 2011.

The effects of beta-sheet breaker peptides KLVFF and LPFFD on the oligomerization of amyloid peptides were studied by all-atom simulations. It was found that LPFFD interferes the aggregation of A β _{16–22} peptides to a greater extent than does KLVFF. Using the molecular mechanics-Poisson–Boltzmann surface area (MM-PBSA) method, we found that the former binds more strongly to A β _{16–22}. Therefore, by simulations, we have clarified the relationship between aggregation rates and binding affinity: the stronger the ligand binding, the slower the oligomerization process.

Free-Energy Landscapes of Protein Domain Movements upon Ligand Binding

Hiroko X. Kondo, Noriaki Okimoto [RIKEN Advanced Science Institute], Gentaro Morimoto, and Makoto Taiji

J. Phys. Chem. B., **115**, 7629–7636, 2011.

The conformation and functions of proteins are closely linked, and many proteins undergo conformational changes upon ligand binding. The X-ray crystallographic studies have revealed conformational differences in proteins between the liganded and unliganded states. Here, we clarified the difference in the mechanisms responsible for the conformational changes induced in two proteins upon ligand binding by examining computationally determined free-energy profiles of the apo- and holoproteins.

Computer simulation study of amyloid fibril formation by palindromic sequences in prion peptides

Victoria A. Wagoner, Mookyung Cheon, Iksoo Chang and Carol K. Hall [Box 7905, COE1, 911 Partners Way]

Proteins: Stru. Fun. and Bioinfo. **79**, 2132–2145, 2011.

We simulate the aggregation of large systems containing palindromic peptides from the Syrian hamster prion protein SHaPrP 113–120 (AGAAAAGA) and the mouse prion protein MoPrP 111–120 (VAGAAAAGAV) and eight sequence variations: GAAAAAAG, (AG)₄, A8, GAAAGAAA, A10, V10, GAVAAAAGAV, and VAVAAAAGAV. The first two peptides are thought to act as the Velcro that holds the parent prion proteins together in amyloid structures and can form fibrils themselves. The ability to form fibrils increases as the chain length and the length of the stretch of hydrophobic residues increase.

Glucose interactions with a model peptide

Phillip E. Mason, Adrien Lerbret, Marie-Louise Saboungi, George W. Neilson, Christopher E. Dempsey and John W. Brady [Cornell University]

Proteins: Stru. Fun. and Bioinfo. **79**, 2224–2232, 2011.

Molecular dynamics simulations have been conducted of the helical polypeptide melittin, in concentrated aqueous solutions of the alpha and beta anomers of D-glucopyranose. Glucose is an osmolyte, and it is expected to be preferentially excluded from the surfaces of proteins. This was indeed found to be the case in the simulations. The results indicate that the observed exclusion may have a contribution from an under-representation of hydrogen bonding interactions between glucose groups and exposed side chains, compared to water.

Protein Dynamics (Cont'd)

The role of tyrosine 71 in modulating the flap conformations of BACE1

Steven A. Spronk [Bristol-Myers Squibb Company] and Heather A. Carlson

Proteins: Stru. Fun. and Bioinfo. **79**, 2247–2259, 2011.

β -site amyloid precursor protein cleaving enzyme 1 (BACE1) is a potential target for treating Alzheimer's disease. BACE1's binding site is partially covered by a flexible loop on its N-terminal domain, known as the "flap," which has been found in several conformations in crystal structures of BACE1 and other aspartyl proteases. The side chain of the invariant residue Tyr71 on the flap adopts several rotameric orientations, leading to our hypothesis that the orientation of this residue dictates the movement and conformations available to the flap. We investigated this hypothesis by performing 220 ns of molecular dynamics simulations of bound and unbound wild-type BACE1 as well as the unbound Y71A mutant.

In silico predictions of LH2 ring sizes from the crystal structure of a single subunit using molecular dynamics simulations

Lorant Janosi, Harindar Keer, Richard J. Cogdell, Thorsten Ritz and Ioan Kosztin [University of Missouri]

Proteins: Stru. Fun. and Bioinfo. **79**, 2306–2315, 2011.

Most of the currently known light-harvesting complexes 2 (LH2) rings are formed by 8 or 9 subunits. As of now, questions like "what factors govern the LH2 ring size?" and "are there other ring sizes possible?" remain largely unanswered. Here, we investigate by means of molecular dynamics (MD) simulations and stochastic modeling the possibility of predicting the size of an LH2 ring from the sole knowledge of the high resolution crystal structure of a single subunit. Starting with single subunits of two LH2 rings with known size, that is, an 8-ring from *Rhodospirillum rubrum* (MOL1) and a 9-ring from *Rhodospirillum rubrum* (ACI), and one with unknown size (referred to as X), we build atomic models of subunit dimers corresponding to assumed 8-, 9-, and 10-ring geometries.

Free Energy Calculations

Accurate Determination of the Binding Free Energy for KcsA-Charybdotoxin Complex from the Potential of Mean Force Calculations with Restraints

Po-Chia Chen, Serdar Kuyucak [University of Sydney]

Biophysical Journal. **100**, 2466–2474, 2011.

Free energy calculations for protein-ligand dissociation have been tested and validated for small ligands (50 atoms or less), but there has been a paucity of studies for larger, peptide-size ligands due to computational limitations. Previously we have studied the energetics of dissociation in a potassium channel-charybdotoxin complex by using umbrella sampling molecular-dynamics simulations, and established the need for carefully chosen coordinates and restraints to maintain the physiological ligand conformation. Here we address the ligand integrity problem further by constructing additional potential of mean forces for dissociation of charybdotoxin using restraints.

Free Energy Calculations (Cont'd)

Calculation of free energy landscapes: A histogram reweighted metadynamics approach

Jens Smiatek [Westfälische Wilhelms-Universität Münster] and Andreas Heuer

J. Comp. Chem. **32**, 2084–2096, 2011.

We present an efficient method for the calculation of free energy landscapes. Our approach involves a history-dependent bias potential, which is evaluated on a grid. The corresponding free energy landscape is constructed via a histogram reweighting procedure a posteriori. Because of the presence of the bias potential, it can be also used to accelerate rare events. In addition, the calculated free energy landscape is not restricted to the actual choice of collective variables and can in principle be extended to auxiliary variables of interest without further numerical effort.

Minimum MD simulation length required to achieve reliable results in free energy perturbation calculations: Case study of relative binding free energies of fructose-1,6-bisphosphatase inhibitors

R.S. Rathore, P. Aparoy, P. Reddanna, A. K. Kondapi and M. Rami Reddy [University of Hyderabad]

J. Comp. Chem. **32**, 2097–2103, 2011.

In an attempt to establish the criteria for the length of simulation to achieve the desired convergence of free energy calculations, two studies were carried out on chosen complexes of FBPase-AMP mimics. Calculations were performed for varied length of simulations and for different starting configurations using both conventional- and QM/MM-FEP methods. The results demonstrate that for small perturbations, 1248 ps simulation time could be regarded a reasonable yardstick to achieve convergence of the results. As the simulation time is extended, the errors associated with free energy calculations also gradually tapers off.

Quantum mechanical binding free energy calculation for phosphopeptide inhibitors of the Lck SH2 domain

Victor M. Anisimov and Claudio N. Cavasotto [University of Texas Health Science Center at Houston]

J. Comp. Chem. **32**, 2254–2263, 2011.

The accurate and efficient calculation of binding free energies is essential in computational biophysics. We present a linear-scaling QM-based end-point method termed MM/QM-COSMO to calculate binding free energies in biomolecular systems, with an improved description of entropic changes. Molecular dynamics trajectories are re-evaluated using a semiempirical Hamiltonian and a continuum solvent model; translational and rotational entropies are calculated using configurational integrals, and internal entropy is calculated using the harmonic oscillator approximation.

A High-Throughput Steered Molecular Dynamics Study on the Free Energy Profile of Ion Permeation through Gramicidin A

Toni Giorgino and Gianni De Fabritiis [Universitat Pompeu Fabra]

J. Chem. Theor. and Comp. **7**, 1943–1950, 2011.

Steered molecular dynamics (SMD) simulations for the calculation of free energies are well suited for high-throughput molecular simulations on a distributed infrastructure due to the simplicity of the setup and parallel granularity of the runs. However, so far, the computational cost limited the estimation of the free energy typically over just a few pullings, thus impeding the evaluation of statistical uncertainties involved. In this work, we performed two thousand pulls for the permeation of a potassium ion in the gramicidin A pore by all-atom molecular dynamics in order to assess the bidirectional SMD protocol with a proper amount of sampling.

Free Energy Calculations (Cont'd)

Paradynamics: An Effective and Reliable Model for Ab Initio QM/MM Free-Energy Calculations and Related Tasks

Nikolay V. Plotnikov, Shina C. L. Kamerlin, and Arieh Warshel [University of Southern California]

J. Phys. Chem. B., **115**, 7950–7962, 2011.

Recent years have seen tremendous effort in the development of approaches with which to obtain QM/MM free energies for reactions in the condensed phase. One popular approach that seems to offer an ideal way to progress is the elegant metadynamics approach. However, in the current work, we point out the subtle efficiency problems associated with this approach and illustrate that we have at hand a more powerful approach. More specifically, we demonstrate the effectiveness of an updated version of our original idea of using a classical reference potential for QM(ai)/MM calculations, which we refer to as paradynamics .

Ligand Binding/Docking

Minimal Encounter Time and Separation Determine Ligand-Receptor Binding in Cell Adhesion

Philippe Robert, Alice Nicolas, Said Aranda-Espinoza, Pierre Bongrand, Laurent Limozin [Aix-Marseille University]

Biophysical Journal. **100**, 2642-2651, 2011.

The binding properties of biomolecules play a crucial role in many biological phenomena, especially cell adhesion. Whereas the attachment kinetics of soluble proteins is considered well known, complex behavior arises when protein molecules are bound to the cell membrane. We probe the hidden kinetics of ligand-receptor bond formation using single-molecule flow chamber assays and Brownian dynamics simulations. We show that, consistent with our recently proposed hypothesis, association requires a minimum duration of contact between the reactive species.

Binding conformation prediction between human acetylcholinesterase and cytochrome c using molecular modeling methods

Songmi Kim, Yuno Lee, Pretina Lazar, Minky Son, Ayoung Baek, Sundarapandian Thangapandian, Na Young Jeong, Young Hyun Yoo, Keun Woo Lee [Gyeongsang National University]

J. Mol.Graph. and Mod., **29**, 996-1005, 2011.

The acetylcholinesterase (AChE) is important to terminate acetylcholine-mediated neurotransmission at cholinergic synapses. The pivotal role of AChE in apoptosome formation through the interactions with cytochrome c (Cyt c) was demonstrated in recent study. In order to investigate the binding conformation between the human AChE (hAChE) and human Cyt c (hCyt c), macro-molecular docking simulation was performed using DOT 2.0 program. Based on these results, we were able to predict the reasonable binding conformation which is indispensable for apoptosome formation.

Experimental and computational studies indicate the mutation of Glu12 to increase the thermostability of oligomeric protease from *Pyrococcus horikoshii*

Dongling Zhan, Weiwei Han [Jilin University] and Yan Feng

J. Mol.Mod., **17**, 1241-1249, 2011.

The intracellular protease from *Pyrococcus horikoshii* (PhpI) is a member of the DJ-1/ThiJ/PfpI superfamily, which is suggested to be involved in cellular protection against environmental stresses. In this study, flexible docking approach was employed to dock the ligand into the active site of PhpI. By analyzing the results, active site architecture and certain key residues responsible for substrate specificity were identified on the enzyme. Our docking result indicates that Glu12 plays an important role in substrate binding.

Ligand Binding / Docking (Cont'd)

Structural analysis of natural killer cell receptor protein 1 (NKR-P1) extracellular domains suggests a conserved long loop region involved in ligand specificity

Žofie Sovová, Rüdiger Ettrich [Academy of Sciences of the Czech Republic], Vladimír Kopecký, Tomáš Pazderka, Kateřina Hofbauerová and Daniel Rozbeský, et al

J. Mol.Mod., **17**, 1353-1370, 2011.

Receptor proteins at the cell surface regulate the ability of natural killer cells to recognize and kill a variety of aberrant target cells. The structural features determining the function of natural killer receptor proteins 1 (NKR-P1s) are largely unknown. In the present work, refined homology models are generated for the C-type lectin-like extracellular domains of rat NKR-P1A and NKR-P1B, mouse NKR-P1A, NKR-P1C, NKR-P1F, and NKR-P1G, and human NKR-P1 receptors. Experimental data on secondary structure, tertiary interactions, and thermal transitions are acquired for four of the proteins using Raman and infrared spectroscopy.

Docking of the alkaloid geissospermine into acetylcholinesterase: a natural scaffold targeting the treatment of Alzheimer's disease

Jocley Queiroz Araújo [Universidade Federal do Rio de Janeiro], Josélia Alencar Lima, Angelo da Cunha Pinto, Ricardo Bicca de Alencastro and Magaly Girão Albuquerque

J. Mol.Mod., **17**, 1401-1412, 2011.

Pharmacological studies from our group [Lima et al. Pharmacol Biochem Behav 92:508, (2009)] revealed that geissospermine (GSP), the major alkaloid of the bark extract of Brazilian *Geissospermum vellosii*, inhibits acetylcholinesterases (AChEs) in the brains of rats and electric eels (*Electrophorus electricus*). However, the binding mode (i.e., conformation and orientation) of this indole-indoline alkaloid into the AChE active site is unknown. Therefore, in order to propose a plausible binding mode between GSP and AChE, which might explain the observed experimental inhibitory activity, we performed comparative automatic molecular docking simulations using the AutoDock and Molegro Virtual Docker (MVD) programs.

The binding properties of the H5N1 influenza virus neuraminidase as inferred from molecular modeling

Michal Raab and Igor Tvaroška [Slovak Academy of Sciences]

J. Mol.Mod., **17**, 1445-1456, 2011.

The avian influenza H5N1 virus has emerged as an important pathogen, causing severe disease in humans. Substrate specificity is crucial for the virus to obtain the ability to spread from avian to human. An investigation of the binding properties of ligands at the molecular level is important for understanding the catalytic mechanism of the avian influenza virus neuraminidase and for designing novel and specific inhibitors of H5N1 neuraminidase. Based on the crystal structure of H5N1, we have characterized the binding properties between sialic acid, methyl 3'sialyllactoside, methyl 6'sialyllactoside and the H5N1 influenza virus neuraminidase using molecular docking and MD simulations.

Molecular dynamics simulations of pro-apoptotic BH3 peptide helices in aqueous medium: relationship between helix stability and their binding affinities to the anti-apoptotic protein Bcl-XL

Dilraj Lama and Ramasubbu Sankararamakrishnan [Indian Institute of Technology Kanpur]

J. Comp. Aided Mol. Des. **25**, 413-426, 2011.

The B-cell lymphoma 2 (Bcl-2) family of proteins regulates the intrinsic pathway of apoptosis. Interactions between specific anti- and pro-apoptotic Bcl-2 proteins determine the fate of a cell. Here, we have studied the relation between the stable helical nature of BH3 peptides and their affinities to Bcl-XL, an anti-apoptotic Bcl-2 protein. We have carried out MD simulations of six BH3 peptides derived from Bak, Bad and Bim pro-apoptotic proteins for a period of 50 ns each in aqueous medium.

Ligand Binding / Docking (Cont'd)

Binding to the open conformation of HIV-1 protease

Katrina W. Lexa and Heather A. Carlson [University of Michigan]

Proteins: Stru. Fun. and Bioinfo. **79**, 2282–2290, 2011.

A recent crystal structure of HIV-1 protease (HIVp) was the first to experimentally observe a ligand targeting an open-flap conformation. Researchers studying a symmetric pyrrolidine inhibitor found that two ligands cocrystallized with the protease, forcing an unusual configuration and unique crystallographic contacts. One molecule is centered in the traditional binding site (α pose) and the other binds between the flaps (β pose). Molecular dynamics simulations were used to examine the solution-state behavior of three possible binding modes: the ternary complex of HIVp+ $\alpha\beta$ and the binary complexes, HIVp+ α and HIVp+ β . We show that HIVp+ α is the most stable of the three states.

Enzyme Catalysis

Combining molecular docking and QSAR studies for modelling the antigrase activity of cyclothialidine derivatives

Liane Saíz-Urra [Universidad Central “Marta Abreu” de las Villas], Miguel Ángel Cabrera Pérez, Aliuska Morales Helguera, Matheus Froeyen

Europ. Jou. Med. Chem., **46**, 2736-2747, 2011.

DNA gyrase is a well-established antibacterial target consisting of two subunits, GyrA and GyrB, in a heterodimer A_2B_2 , where GyrB catalyzes the hydrolysis of ATP. Cyclothialidine (Ro 09-1437) has been considered as a promising inhibitor whose modifications might lead to more potent compounds against the enzyme. We report here for the first time, QSAR studies regarding to ATPase inhibitors of DNA Gyrase. 1D, 2D and 3D descriptors from DRAGON software were used on a set of 42 cyclothialidine derivatives.

Tightening of Active Site Interactions En Route to the Transition State Revealed by Single-Atom Substitution in the Guanosine-Binding Site of the Tetrahymena Group I Ribozyme

Marcello Forconi, Rishi H. Porecha, Joseph A. Piccirilli, and Daniel Herschlag [Stanford University, Stanford]

J. Am. Chem. Soc., **133**, 7791–7800, 2011.

Protein enzymes establish intricate networks of interactions to bind and position substrates and catalytic groups within active sites, enabling stabilization of the chemical transition state. Crystal structures of several RNA enzymes also suggest extensive interaction networks, despite RNA's structural limitations, but there is little information on the functional and the energetic properties of these inferred networks. We used double mutant cycles and presteady-state kinetic analyses to probe the putative interaction between the exocyclic amino group of the guanosine nucleophile and the N7 atom of residue G264 of the Tetrahymena group I ribozyme.

Enzyme Catalysis (Cont'd)

The Need for Enzymatic Steering in Abietic Acid Biosynthesis: Gas-Phase Chemical Dynamics Simulations of Carbocation Rearrangements on a Bifurcating Potential Energy Surface

Matthew R. Siebert, Jiaxu Zhang, Srirangam V. Addepalli, Dean J. Tantillo, and William L. Hase [Texas Tech University]

J. Am. Chem. Soc., **133**, 8335–8343, 2011.

Abietic acid, a constituent of pine resin, is naturally derived from abietadiene—a process that requires four enzymes. In previous work (*Nature Chem.* **2009**, 1, 384), electronic structure calculations on carbocation rearrangements leading to abietadienyl cation revealed an interesting potential energy surface with a bifurcating reaction pathway, which links two products—one natural and one not yet isolated from Nature. Herein we describe direct dynamics simulations of the key step in the formation of abietadiene. The simulations reveal that abietadiene synthase must intervene in order to produce abietadiene selectively, in essence steering this reaction to avoid the generation of byproducts with different molecular architectures.

Application of a ligand-based theoretical approach to derive conversion paths and ligand conformations in CYP11B2-mediated aldosterone formation

Luc Roumen, Bram Van Hoof, Koen Pieterse, Peter A.J. Hilbers, Erica M.G. Custers, Ralf Plate, Marcel De Gooyer, Ilona P.E. Beugels, Judith M.A. Emmen, Dirk Leysen, Jos F.M. Smits, Harry C.J. Ottenheijm and J.J. Rob Hermans [Eindhoven University of Technology]

J. Comp. Chem. **32**, 2441–2448, 2011.

The biosynthesis of the mineralocorticoid hormone aldosterone involves a multistep hydroxylation of 11-deoxycorticosterone at the 11- and 18-positions, resulting in the formation of corticosterone and 18-hydroxycorticosterone, the final precursor of aldosterone. Two members of the cytochrome P450 11B family, CYP11B1 and CYP11B2, are known to catalyze these 11- and 18-hydroxylations, however, only CYP11B2 can oxidize 18-hydroxycorticosterone to aldosterone. It is unknown what sequence of hydroxylations leads to the formation of 18-hydroxycorticosterone. In this study we have investigated which of the possible conversion paths towards formation of 18-hydroxycorticosterone and aldosterone are most likely from the ligand perspective.

Probing the reactivation process of sarin-inhibited acetylcholinesterase with α -nucleophiles: Hydroxylamine anion is predicted to be a better antidote with DFT calculations

Md Abdul Shafeeuulla Khan, Rabindranath Lo, Tusar Bandyopadhyay, Bishwajit Ganguly [Central Salt & Marine Chemicals Research Institute, Bhavnagar]

J. Mol. Graph. and Mod., **29**, 1039–1046, 2011.

Inactivation of acetylcholinesterase (AChE) due to inhibition by organophosphorus (OP) compounds is a major threat to human since AChE is a key enzyme in neurotransmission process. Oximes are used as potential reactivators of OP-inhibited AChE due to their α -effect nucleophilic reactivity. In search of more effective reactivating agents, model studies have shown that α -effect is not so important for dephosphorylation reactions. We report the importance of α -effect of nucleophilic reactivity towards the reactivation of OP-inhibited AChE with hydroxylamine anion. We have demonstrated with DFT [B3LYP/6-311G(d,p)] calculations that the reactivation process of sarin–serine adduct 2 with hydroxylamine anion is more efficient than the other nucleophiles reported.

Enzyme Catalysis (Cont'd)

Molecular Modeling and Molecular Dynamics Simulation Studies of the GSK3 β /ATP/Substrate Complex: Understanding the Unique P+4 Primed Phosphorylation Specificity for GSK3 β Substrates

Shao-Yong Lu, Yong-Jun Jiang [Zhejiang University], Jian-Wei Zou, and Tian-Xing Wu

J.Chem. Infor. and Mod. **51**, 1025–1036, 2011.

Substrate specificity of protein kinases is of fundamental importance for the integrity and fidelity of signaling pathways. Glycogen synthase kinase 3 β (GSK3 β) has a unique substrate specificity that prefers phosphorylation of its substrates at the P+4 serine before it can further phosphorylate the substrate at the P0 serine in the canonical motif SXXXS(p), where S(p) is the primed phosphorylation site. Here, 3D model of the ternary complex of GSK3 β , ATP, and the phosphorylated glycogen synthase (pGS), termed GSK3 β /ATP/pGS, is constructed using a hierarchical approach and by integrating molecular modeling and MD simulations.

Inhibitor and Substrate Binding by Angiotensin-Converting Enzyme: Quantum Mechanical/Molecular Mechanical Molecular Dynamics Studies

Xuemei Wang, Shanshan Wu, Dingguo Xu [Sichuan University], Daiqian Xie, and Hua Guo

J.Chem. Infor. and Mod. **51**, 1074–1082, 2011.

Angiotensin-converting enzyme (ACE) is an important zinc-dependent hydrolase responsible for converting the inactive angiotensin I to the vasoconstrictor angiotensin II and for inactivating the vasodilator bradykinin. However, the substrate binding mode of ACE has not been understood. Here, we propose a model for an ACE Michaelis complex based on two known X-ray structures of inhibitor-enzyme complexes. Specifically, the human testis angiotensin-converting enzyme (tACE) complexed with two clinic drugs were first investigated using a combined QM/MM approach.

Secretory Phospholipase A₂ Activity toward Diverse Substrates

Jesper J. Madsen, Lars Linderöth, Arun K. Subramanian, Thomas L. Andresen, and Gunther H. Peters [Technical University of Denmark]

J. Phys. Chem. B., **115**, 6853–6861, 2011.

We have studied secretory phospholipase A₂-IIA (sPLA₂) activity toward different phospholipid analogues by performing biophysical characterizations and MD simulations. The phospholipids were natural substrates, triple alkyl phospholipids, a prodrug anticancer etherlipid, and an inverted ester. The latter were included to study head group–enzyme interactions. Our simulation results show that the lipids are optimally placed into the binding cleft and that water molecules can freely reach the active site through a well-defined pathway; both are indicative that these substrates are efficiently hydrolyzed, which is in good agreement with our experimental data.

Crystal structure of a metal-dependent phosphoesterase (YP_910028.1) from *Bifidobacterium adolescentis*: Computational prediction and experimental validation of phosphoesterase activity

Gye Won Han, Jaeju Ko, Carol L. Farr, Marc C. Deller, Qingping Xu, Hsiu-Ju Chiu, Mitchell D. Miller, Jana Sefcikova, Srinivas Somarowthu, Penny J. Beuning, Marc-André Elsliger, Ashley M. Deacon, Adam Godzik, Scott A. Lesley, Ian A. Wilson and Mary Jo Ondrechen [Northeastern University, 360 Huntington Ave., 102 HT, Boston]

Proteins: Stru. Fun. and Bioinfo. **79**, 2146–2160, 2011.

The crystal structures of an unliganded and adenosine 5'-monophosphate (AMP) bound, metal-dependent phosphoesterase (YP_910028.1) from *Bifidobacterium adolescentis* are reported at 2.4 and 1.94 Å, respectively. Functional characterization of this enzyme was guided by computational analysis and then confirmed by experiment. The structure consists of a polymerase and histidinol phosphatase (PHP, Pfam: PF02811) domain with a second domain (residues 105-178) inserted in the middle of the PHP sequence. The results suggest that many of the sequence neighbors previously annotated as having DNA polymerase activity may actually be misannotated.

Protein-Protein Interactions

PLIO: an ontology for formal description of protein–ligand interactions

Olga Ivchenko, Erfan Younesi, Mohammad Shahid, Antje Wolf, Bernd Müller, and Martin Hofmann-Apitius [Fraunhofer Institute for Algorithms and Scientific Computing]

Bioinformatics. **27**, 1684-1690, 2011.

The protein–ligand interaction ontology (PLIO) was developed around three main concepts, namely target, ligand and interaction, and was enriched by adding synonyms, useful annotations and references. The quality of the ontology was assessed based on structural, functional and usability features. Validation of the lexicalized ontology by means of natural language processing (NLP)-based methods showed a satisfactory performance (F-score = 81%). The usefulness of PLIO is demonstrated by two use-case scenarios and it is shown that PLIO is able to capture both confirmatory and new knowledge from simulation and empirical studies.

Elucidating glycosaminoglycan–protein–protein interactions using carbohydrate microarray and computational approaches

Claude J. Rogers, Peter M. Clark, Sarah E. Tully, Ravinder Abrol, K. Christopher Garcia, William A. Goddard III, and Linda C. Hsieh-Wilson [Howard Hughes Medical Institute]

PNAS. **108**, 9747-9752, 2011.

Glycosaminoglycan polysaccharides play critical roles in many cellular processes, ranging from viral invasion and angiogenesis to spinal cord injury. Their diverse biological activities are derived from an ability to regulate a remarkable number of proteins. However, few methods exist for the rapid identification of glycosaminoglycan–protein interactions and for studying the potential of glycosaminoglycans to assemble multimeric protein complexes. Here, we report a multidisciplinary approach that combines new carbohydrate microarray and computational modeling methodologies to elucidate glycosaminoglycan–protein interactions.

Membrane Proteins and Lipid Peptide Interactions

Comparison of thermal effects of stilbenoid analogs in lipid bilayers using differential scanning calorimetry and molecular dynamics: correlation of thermal effects and topographical position with antioxidant activity

Catherine Koukoulitsa, Serdar Durdagi, Eleni Siapi, Thomas Mavromoustakos [University of Athens], Carolina Villalonga-Barber and Xanthippi Alexi, et al.

Europ. Biophys. Jou., **40**, 865-875, 2011.

In previous studies it was shown that cannabinoids (CBs) bearing a phenolic hydroxyl group modify the thermal properties of lipid bilayers more significantly than methylated congeners. In this work the thermal effects of synthetic polyphenolic stilbenoid analogs and their methylated congeners have been studied using differential scanning calorimetry (DSC). Molecular dynamics (MD) simulations have been performed to explain the DSC results. Thus, two of their phenolic hydroxyl groups orient in the lipid bilayers in such a way that they anchor in the region of the head-group. In contrast, their methoxy congeners cannot anchor effectively and are embedded deeper in the hydrophobic segment of the lipid bilayers.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Enantiomeric Segregation in the Gel Phase of Lipid Bilayers

Bruno A. C. Horta [Swiss Federal Institute of Technology] and Philippe H. Honenberger

J. Am. Chem. Soc., **133**, 8464–8466, 2011.

Enantiospecific interactions within a monoglyceride lipid bilayer are investigated using molecular dynamics simulations. Preferential homochiral interactions are observed in the gel phase, whereas no detectable enantiospecificity is seen in the liquid-crystal phase. On the basis of these results and available experimental data, a mechanism is proposed for the formation of the coagel phase of monoglycerides. Enantiomeric segregation in the gel phase is also discussed in terms of its possible implications for prebiological evolution and membrane raft function.

Inter-ring rotation of apolipoprotein A-I protein monomers for the double-belt model using biased molecular dynamics

Thomas R. Caulfield [Georgia Institute of Technology]

J. Mol. Graph. and Mod., **29**, 1006–1014, 2011.

The double belt model for lipid-bound discoidal apolipoprotein A-I consists of two alpha-helical monomers bound about a unilamellar bilayer of lipids. Previous work, based on salt bridge calculations, has demonstrated that the L5/5 registration, Milano mutant, and Paris mutant are preferred conformations for apolipoprotein A-I. The Paris (R151C) and Milano (R173C) mutants indicate a mode of change must be available. Here, we present computational data for independent inter-ring rotation of the two alpha-helical monomers about the lipid unilamellar bilayer core. The simulations presented here support the existing double-belt model.

CELLmicrocosmos 2.2 MembraneEditor: A Modular Interactive Shape-Based Software Approach To Solve Heterogeneous Membrane Packing Problems

Bjorn Sommer [Bielefeld University], Tim Dingersen, Christian Gamroth, Sebastian E. Schneider, Sebastian Rubert, Jens Kruger, and Karl-Josef Dietz

J. Chem. Infor. and Mod., **51**, 1165–1182, 2011.

New perspectives have been developed to understand the processes of modeling heterogeneous membranes. These are crucial steps prior to applying advanced techniques like molecular dynamic simulations of whole membrane systems. Lipid, protein, and membrane packing problems are addressed based on biochemical properties in combination with computational optimization techniques. The CELLmicrocosmos 2.2 MembraneEditor (CmME) is introduced as an appropriate framework to handle such problems by offering diverse algorithmic approaches. Its algorithm plug-in-interface enables modelers to generate problem-specific algorithms.

Dynamic information for cardiotoxin protein desorption from a methyl-terminated self-assembled monolayer using steered molecular dynamics simulation

Shih-Wei Hung [National Tsing Hua University], Pai-Yi Hsiao, and Ching-Chang Chieng

Jou. Chem. Phys., **134**, 194705, 2011.

Dynamic information, such as force, structural change, interaction energy, and potential of mean force (PMF), about the desorption of a single cardiotoxin (CTX) protein from a methyl-terminated self-assembled monolayer (SAM) surface was investigated by means of steered molecular dynamics (SMD) simulations. The simulation results indicated that Loop I is the first loop to depart from the SAM surface, which is in good agreement with the results of the nuclear magnetic resonance spectroscopy experiment.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Lipid Membranes with a Majority of Cholesterol: Applications to the Ocular Lens and Aquaporin 0

Joseph W. O'Connor and Jeffery B. Klauda [University of Maryland]

J. Phys. Chem. B., **115**, 6455–6464, 2011.

Using molecular dynamics (MD) simulations, we studied the structure and dynamics of two dimyristoylphosphatidylcholine (DMPC):cholesterol bilayers at concentrations representative of the ocular lens (ratios of 1:1 and 1:2). These MD simulations agree well with experimental deuterium order parameters and bilayer peak-to-peak distances. Although it is known that the average surface area per lipid rapidly decreases from low to moderate levels of cholesterol, our simulations indicate that there is a relatively small change in the average lipid area from 50 to 66.7% cholesterol (40.5 ± 0.2 and $39.5 \pm 0.1 \text{ \AA}^2/\text{lipid}$, respectively).

Capturing Spontaneous Partitioning of Peripheral Proteins Using a Biphasic Membrane-Mimetic Model

Mark J. Arcario, Y. Zenmei Ohkubo, and Emad Tajkhorshid [University of Illinois at Urbana-Champaign]

J. Phys. Chem. B., **115**, 7029–7037, 2011.

Membrane binding of peripheral proteins, mediated by specialized anchoring domains, is a crucial step for their biological function. Computational studies of membrane insertion, however, have proven challenging and largely inaccessible. Here, we address some of these issues by developing and employing a simplified representation of the membrane by a biphasic solvent model which we demonstrate can be used efficiently to capture and describe the process of hydrophobic insertion of membrane anchoring domains in all-atom molecular dynamics simulations.

Quantifying Water-Mediated Protein–Ligand Interactions in a Glutamate Receptor: A DFT Study

Michelle A. Sahai and Philip C. Biggin [University of Oxford]

J. Phys. Chem. B., **115**, 7085–7096, 2011.

It is becoming increasingly clear that careful treatment of water molecules in ligand–protein interactions is required in many cases if the correct binding pose is to be identified in molecular docking. Water can form complex bridging networks and can play a critical role in dictating the binding mode of ligands. Despite possessing similar chemical moieties, crystal structures of glutamate and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) in complex with the ligand-binding core of the GluA2 ionotropic glutamate receptor revealed, contrary to all expectation, two distinct modes of binding. The difference appears to be related to the position of water molecules within the binding pocket.

Clusters of Proteins in Biomembranes: Insights into the Roles of Interaction Potential Shapes and of Protein Diversity

Nicolas Meilhac [Universite de Toulouse] and Nicolas Destainville

J. Phys. Chem. B., **115**, 7190–7199, 2011.

It has recently been proposed that proteins embedded in lipidic biomembranes can spontaneously self-organize into stable small clusters, or membrane nanodomains, due to the competition between short-range attractive and longer-range repulsive forces between proteins, specific to these systems. In this paper, we carry on our investigation, by Monte Carlo simulations, of different aspects of cluster phases of proteins in biomembranes. We confirm theoretical predictions in terms of biological cluster specialization by deciphering how clusters recruit only a few protein species.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Gramicidin A Backbone and Side Chain Dynamics Evaluated by Molecular Dynamics Simulations and Nuclear Magnetic Resonance Experiments. I: Molecular Dynamics Simulations

Helgi I. Ingolfsson, Yuhui Li, Vitaly V. Vostrikov, Hong Gu, James F. Hinton, Roger E. Koeppe, II, Benoit Roux, and Olaf S. Andersen [Weill Cornell Medical College]

J. Phys. Chem. B., **115**, 7417–7426, 2011.

Gramicidin A (gA) channels provide an ideal system to test molecular dynamics (MD) simulations of membrane proteins. The peptide backbone lines a cation-selective pore, and due to the small channel size, the average structure and extent of fluctuations of all atoms in the peptide will influence ion permeation. This raises the question of how well molecular mechanical force fields used in MD simulations and potential of mean force (PMF) calculations can predict structure and dynamics as well as ion permeation. To address this question, we undertook a comparative study of nuclear magnetic resonance (NMR) observables predicted by fully atomistic MD simulations on a gA dimer embedded in a sodium dodecyl sulfate (SDS) micelle with measurements of the gA dimer backbone and tryptophan side chain dynamics using solution-state ^{15}N NMR on gA dimers in SDS micelles.

Protein Folding

Structural Basis of Folding Cooperativity in Model Proteins: Insights from a Microcanonical Perspective

Tristan Bereau, Markus Deserno, Michael Bachmann [Carnegie Mellon University]

Biophysical Journal. **100**, 2764-2772, 2011.

Two-state cooperativity is an important characteristic in protein folding. It is defined by a depletion of states that lie energetically between folded and unfolded conformations. Here, we present a detailed characterization of several helical peptides obtained by coarse-grained simulations. The level of resolution of the coarse-grained model allowed to study realistic structures ranging from small α -helices to a de novo three-helix bundle without biasing the force field toward the native state of the protein.

Observation of Two Families of Folding Pathways of BBL

Jue Fan, Mojie Duan, Da-Wei Li, Hao Wu, Haijun Yang, Li Han, Shuanghong Huo [Clark University]

Biophysical Journal. **100**, 2457-2465, 2011.

BBL is an independent folding domain of a large multienzyme complex, 2-oxoglutarate dehydrogenase. The folding mechanism of BBL is under debate between the views of noncooperative downhill-type and classical two-state. Extensive replica exchange molecular dynamics simulations of BBL in explicit solvent have shown some non-two-state behaviors despite no definitive evidence of downhill folding. In this work, we postprocess the replica exchange data using our roadmap-based MaxFlux reaction path algorithm to reveal atomically detailed folding pathways. A connected graph is used to organize and visualize the folding pathways initiated from random coils.

Protein Folding (Cont'd)

Combination of Markov State Models and Kinetic Networks for the Analysis of Molecular Dynamics Simulations of Peptide Folding

Isolde H. Radford, Alan R. Fersht, and Giovanni Settanni
[MRC – Centre for Protein Engineering]

J. Phys. Chem. B., **115**, 7459–7471, 2011.

Atomistic molecular dynamics simulations of the TZ1 beta-hairpin peptide have been carried out using an implicit model for the solvent. The trajectories have been analyzed using a Markov state model defined on the projections along two significant observables and a kinetic network approach. The Markov state model allowed for an unbiased identification of the metastable states of the system, and provided the basis for commitment probability calculations performed on the kinetic network.

Folding of Small Proteins Using Constrained Molecular Dynamics

Gouthaman S. Balaraman, In-Hee Park, Abhinandan Jain, and Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Phys. Chem. B., **115**, 7588–7596, 2011.

The focus of this paper is to examine whether conformational search using constrained MD method is more enhanced and enriched toward “native-like” structures compared to all-atom MD for the protein folding as a model problem. Constrained MD methods provide an alternate MD tool for protein structure prediction and structure refinement. It is computationally expensive to perform all-atom simulations of protein folding because the processes occur on a time scale of microseconds. Compared to the all-atom MD simulation, constrained MD methods have the advantage that stable dynamics can be achieved for larger time steps and the number of degrees of freedom is an order of magnitude smaller, leading to a decrease in computational cost.

Protein-Nucleic acid Interactions

Computer- and structure-based lead design for epigenetic targets

Ralf Heinke, Luca Carlino, Srinivasaraghavan Kannan, Manfred Jung, Wolfgang Sippl [Martin-Luther University of Halle-Wittenberg]

Bioorg. and Med.Chem., **19**, 3605–3615, 2011.

The term epigenetics is defined as inheritable changes that influence the outcome of a phenotype without changes in the genome. Epigenetics is based upon DNA methylation and posttranslational histone modifications. While there is much known about reversible acetylation as a posttranslational modification, research on reversible histone methylation is still emerging, especially with regard to drug discovery. This article will summarize the progress on small molecule epigenetic inhibitors identified by structure- and computer-based approaches.

Molecular Dynamics Simulations of DNA/PEI Complexes: Effect of PEI Branching and Protonation State

Chongbo Sun, Tian Tang [University of Alberta, Edmonton], Hasan Uludağ, Javier E. Cuervo

Biophysical Journal. **100**, 2754–2763, 2011.

Complexes formed by DNA and polyethylenimine (PEI) are of great research interest because of their application in gene therapy. In this work, we carried out all-atom molecular dynamics simulations to study eight types of DNA/PEI complexes, each of which was formed by one DNA duplex d(CGCGAATTGCG)₂ and one PEI. We used eight different PEIs with four different degrees of branching and two protonation ratios of amine groups (23% and 46%) in the simulations to investigate how the branching degree and protonation state can affect the binding.

Protein-Nucleic acid Interactions (Cont'd)

Evaluation of DNA binding, DNA cleavage, protein binding and in vitro cytotoxic activities of bivalent transition metal hydrazone complexes

P. Krishnamoorthy, P. Sathyadevi, Alan H. Cowley, Rachel R. Butorac, N. Dharmaraj [University of Texas at Austin]

Europ. Jou. Med. Chem., **46**, 3376-3387, 2011.

Divalent Co, Ni and Cu hydrazone complexes containing [N'-(phenyl(pyridine-2-yl)methylidene) benzohydrazide] ligand were synthesised and characterised. Interactions of these complexes with DNA revealed an intercalative mode of binding between them. Further, all the hydrazone chelates showed moderate ability to cleave pUC19 DNA. Synchronous fluorescence spectra proved that the interaction of metal complexes with bovine serum albumin (BSA) resulted in a conformational change of the latter.

The Role of RNA Sequence and Structure in RNA-Protein Interactions

Aditi Gupta, Michael Gribskov [Purdue University]

J. Molec. Bio. **407**, 574-587, 2011.

We investigate the sequence and structural properties of RNA-protein interaction sites in 211 RNA-protein chain pairs, the largest set of RNA-protein complexes analyzed to date. Statistical analysis confirms and extends earlier analyses made on smaller data sets. There are 24.6% of hydrogen bonds between RNA and protein that are nucleobase specific, indicating the importance of both nucleobase-specific and -nonspecific interactions. This study shows strong preferences for both RNA bases and RNA structural states in protein-RNA interactions, indicating their mutual importance in protein recognition.

Nucleic Acids

Computational approaches to RNA structure prediction, analysis, and design

Christian Laing, Tamar Schlick [New York University]

Curr. Opin. Stru. Biol., **15**, 306-318, 2011.

RNA molecules are important cellular components involved in many fundamental biological processes. Understanding the mechanisms behind their functions requires RNA tertiary structure knowledge. Here, we review recent advances in RNA folding algorithms, RNA tertiary motif discovery, applications of graph theory approaches to RNA structure and function, and in silico generation of RNA sequence pools for aptamer design. Advances within each area can be combined to impact many problems in RNA structure and function.

Catalytic Mechanism of RNA Backbone Cleavage by Ribonuclease H from Quantum Mechanics/Molecular Mechanics Simulations

Edina Rosta, Marcin Nowotny, Wei Yang, and Gerhard Hummer [National Institutes of Health, Bethesda]

J. Am. Chem. Soc., **133**, 8934-8941, 2011.

We use QM/MM simulations to study the cleavage of the ribonucleic acid (RNA) backbone catalyzed by ribonuclease H. This protein is a prototypical member of a large family of enzymes that use two-metal catalysis to process nucleic acids. By combining Hamiltonian replica exchange with a finite-temperature string method, we calculate the free energy surface underlying the RNA-cleavage reaction and characterize its mechanism. We find that the reaction proceeds in two steps. Proton-transfer reactions and changes in the metal ion coordination emerge as central factors in the RNA-cleavage reaction.

Nucleic Acids (Cont'd)

Automated RNA tertiary structure prediction from secondary structure and low-resolution restraints

Matthew G. Seetin and David H. Mathews [University of Rochester Medical Center]

J. Comp. Chem. **32**, 2232–2244, 2011.

A novel protocol for all-atom RNA tertiary structure prediction is presented that uses restrained molecular mechanics and simulated annealing. The restraints are from secondary structure, covariation analysis, coaxial stacking predictions for helices in junctions, and, when available, cross-linking data. Results are demonstrated on the Alu domain of the mammalian signal recognition particle RNA, the *Saccharomyces cerevisiae* phenylalanine tRNA, the hammerhead ribozyme, the hepatitis C virus internal ribosomal entry site, and the P4–P6 domain of the *Tetrahymena thermophila* group I intron.

Molecular dynamics study of solvation effect on diffusivity changes of DNA fragments

Kentaro Doi [Osaka University], Takamasa Uemura and Satoyuki Kawano

J. Mol.Mod., **17**, 1457–1465, 2011.

DNA sequence analyzing and base pair separation techniques have attracted much attention, such as denaturing gradient gel electrophoresis, temperature gradient gel electrophoresis, and capillary electrophoresis. However, details of sequence separation mechanisms in electrophoresis are not clarified enough. In the present study, we theoretically discuss the relationship between diffusivity and hydrated structures of DNA fragments in water solvent using molecular dynamics methods.

Surfaces, Catalysts, and Materials Subjects

Molecular dynamics simulations of ionic and nonionic surfactant micelles with a generalized born implicit-solvent model

Yuhang Wang, Jason A. Wallace, Peter H. Koenig and Jana K. Shen [University of Oklahoma]

J. Comp. Chem. **32**, 2348–2358, 2011.

In recent years, all-atom and coarse-grained models have been developed and applied to simulations of micelles and biological membranes. Here, we explore the question of whether a combined all-atom representation of surfactant molecules and continuum description of solvent based on the generalized Born model can be used to study surfactant micelles. Specifically, we report the parameterization of the GBSW model with a surface-area dependent nonpolar solvation energy term for dodecyl sulfate, dodecyl tetramethylammonium, and dodecyl triethyleneglycol ether molecules.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Ensemble QSAR: A QSAR method based on conformational ensembles and metric descriptors

Raghuvir R. S. Pissurlenkar, Vijay M. Khedkar, Radhakrishnan P. Iyer and Evans C. Coutinho [Bombay College of Pharmacy, Kalina]

J. Comp. Chem. **32**, 2204–2218, 2011.

Quantitative structure–activity relationship (QSAR) is the most versatile tool in computer-assisted molecular design. One conceptual drawback seen in QSAR approaches is the “one chemical–one structure–one parameter value” dogma where the model development is based on physicochemical description for a single molecular conformation, while ignoring the rest of the conformational space. As a step toward understanding the role of the discrete microscopic states in biological activity, we have put together a theoretically rigorous and computationally tractable formalism coined as eQSAR.

Potentials and Parameters

Parameterization of Org27569: An allosteric modulator of the cannabinoid CB₁ G protein-coupled receptor

Hadley A. Iliff, Diane L. Lynch, Evangelia Kotsikorou and Patricia H. Reggio [University of North Carolina at Greensboro]

J. Comp. Chem. **32**, 2119–2126, 2011.

The cannabinoid CB₁ receptor is a class A G protein-coupled receptor (GPCR) that is the most widely expressed GPCR in the brain. While both endogenous and synthetic ligands that act at the CB₁ orthosteric site have been known for some time, compounds that act at a CB₁ allosteric site have only recently been discovered. The most studied of these is 5-chloro-3-ethyl-1H-indole-2-carboxylic acid [2-(4-piperidin-1-ylphenyl)ethyl]amide (Org27569). We present the development of missing CHARMM force field parameters for Org27569 using previously published methods and the validation and application of these new parameters using normal mode analysis and molecular dynamics simulations combined with experimental infrared measurements.

Molecular dynamics simulations and free energy calculations on the enzyme 4-hydroxyphenylpyruvate dioxygenase

Stephanie B. A. De Beer, Alice Glättli, Johannes Hutzler, Nico P. E. Vermeulen and Chris Oostenbrink [Vrije Universiteit]

J. Comp. Chem. **32**, 2160–2169, 2011.

4-Hydroxyphenylpyruvate dioxygenase is a relevant target in both pharmaceutical and agricultural research. We report on molecular dynamics simulations and free energy calculations on this enzyme, in complex with 12 inhibitors for which experimental affinities were determined. We applied the thermodynamic integration approach and the more efficient one-step perturbation. Even though simulations seem well converged and both methods show excellent agreement between them, the correlation with the experimental values remains poor. We investigate the effect of slight modifications on the charge distribution of these highly conjugated systems and find that accurate models can be obtained when using improved force field parameters.

Potentials and Parameters (Cont'd)

Conformational state-specific free energy differences by one-step perturbation: Protein secondary structure preferences of the GROMOS 43A1 and 53A6 force fields

Zhixiong Lin, Wilfred F. Van Gunsteren and Haiyan Liu [University of Science and Technology of China]

J. Comp. Chem. **32**, 2290–2297, 2011.

The one-step free energy perturbation approach can be applied to obtain conformational state-specific free energy differences (FEDs) associated with changes in force field parameters, and thus offers the possibility to consider conformational equilibria during force field parameterization. In this work, using the alanine decapeptide in explicit water solution as a model, the α -helical and β -hairpin state-specific FEDs associated with force field changes between two widely used parameter sets of the GROMOS force field, namely, 43A1 and 53A6, were determined using one-step perturbation.

Optimization of Coarse-Grained Interaction Potential: Inside Inherent Limitations of Coarse-Graining Methods

Piotr Kowalczyk, Piotr A. Gauden [Curtin University of Technology], and Alina Ciach

J. Phys. Chem. B., **115**, 6985–6994, 2011.

We studied the inherent limitations of coarse-grained (CG) potentials within the recently developed approach (Kowalczyk et al. *J. Phys. Chem. B* **2009**, 113, 12988–12998). For all studied fluids, the spherically symmetric CG potential constructed according to our scheme modified in this work balances the reproduction of various equilibrium properties (i.e., structural and thermodynamic) measured in CG simulations. A general conclusion from our study is the following: an increase in the protic character of a fluid leads to an increase of inherent loss of atomistic details at the CG level.

On the Role of London Dispersion Forces in Biomolecular Structure Determination

Michal Kolar, Tomas Kubar, and Pavel Hobza [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **115**, 8038–8046, 2011.

A DNA dodecamer and the methyladenine...methylthymine (mA...mT) complex in aqueous environment have been studied by means of molecular dynamics simulation, with a modified force field accounting for the hypothetical absence of London dispersion forces. Under these conditions, the mA...mT complex is preserved, while the double-helical DNA oligomer passes via an extended, ladder-like intermediate to a collapsed structure. The results are interpreted in terms of stability and specificity of the structure of studied complexes.

Solvation Energy

Absolute pK_a Values and Solvation Structure of Amino Acids from Density Functional Based Molecular Dynamics Simulation

Martina Mangold, Leslie Rolland, Francesca Costanzo, Michiel Sprik, Marialore Sulpizi, and Jochen Blumberger [University College London]

J. Chem. Theor. and Comp, **7**, 1695–1703, 2011.

Absolute pK_a values of the amino acid side chains of arginine, aspartate, cysteine, histidine, and tyrosine; the C- and N-terminal group of tyrosine; and the tryptophan radical cation are calculated using a revised density functional based molecular dynamics simulation technique introduced previously [Cheng, J.; Sulpizi, M.; Sprik, M. *J. Chem. Phys.* 2009, 131, 154504]. In the revised scheme, acid deprotonation is considered as a dissociation rather than a proton transfer reaction, and a correction term for treating the proton as a hydronium ion is suggested.

Molecular Dynamics

The Molecular Basis for Antimicrobial Activity of Pore-Forming Cyclic Peptides

Anna D. Cirac, Gemma Moiset, Jacek T. Mika, Armagan Koçer, Pedro Salvador, Bert Poolman, Siewert J. Marrink, Durba Sengupta [University of Groningen]

Biophysical Journal. **100**, 2422-2431, 2011.

The mechanism of action of antimicrobial peptides is, to our knowledge, still poorly understood. To probe the biophysical characteristics that confer activity, we present here a molecular-dynamics and biophysical study of a cyclic antimicrobial peptide and its inactive linear analog. In the simulations, the cyclic peptide caused large perturbations in the bilayer and cooperatively opened a disordered toroidal pore, 1–2 nm in diameter. Electrophysiology measurements confirm discrete poration events of comparable size.

A Model for Segregation of Chromatin after Replication: Segregation of Identical Flexible Chains in Solution

Ron Dockhorn [Leibniz Institute of Polymer Research Dresden], Jens-Uwe Sommer

Biophysical Journal. **100**, 2539-2547, 2011.

We study the segregation of two long chains from parallel but randomly twisted start conformations under good solvent conditions using Monte Carlo simulations to mimic chromatin segregation after replication in eukaryotic cells in the end of prophase. To measure the segregation process, we consider the center-of-mass separation between the two chains and the average square distance between the monomers which were connected before segregation starts. We argue that segregation is dominated by free diffusion of the chains, assuming that untwisting can be achieved by Rouse-like fluctuations on the length scale of a twisted loop.

Efficiency of tabu-search-based conformational search algorithms

Christoph Grebner, Johannes Becker, Svetlana Stepanenko and Bernd Engels [Institut für Physikalische und Theoretische Chemie]

J. Comp. Chem. **32**, 2245–2253, 2011.

Efficient conformational search or sampling approaches play an integral role in molecular modeling, leading to a strong demand for even faster and more reliable conformer search algorithms. This article compares the efficiency of a molecular dynamics method, a simulated annealing method, and the basin hopping (BH) approach (which are widely used in this field) with a previously suggested tabu-search-based approach called gradient only tabu search (GOTS).

Constant pH Molecular Dynamics in Explicit Solvent with λ -Dynamics

Serena Donnini, Florian Tegeler, Gerrit Groenhof, and Helmut Grubmoller [Max Planck Institute for Biophysical Chemistry]

J. Chem. Theor. and Comp, **7**, 1962–1978, 2011.

pH is an important parameter in condensed-phase systems, because it determines the protonation state of titratable groups and thus influences the structure, dynamics, and function of molecules in solution. Here, we present a method, implemented within the MD package GROMACS, for constant pH molecular dynamics simulations in explicit solvent that is based on the λ -dynamics approach. The accuracy of the method is tested against titration curves of single amino acids and a dipeptide in explicit solvent.

Molecular Dynamics (Cont'd)

Excited State Dynamics of the Green Fluorescent Protein on the Nanosecond Time Scale

Gabriella Jonasson, Jean-Marie Teuler, Germain Vallverdu, Fabienne Merola, Jacqueline Ridard, Bernard Levy, and Isabelle Demachy [Universite Paris-Sud 11]

J. Chem. Theor. and Comp, 7, 1990–1997, 2011.

We have introduced a new algorithm in the parallel processing PMEMD module of the AMBER suite that allows MD simulations with a potential involving two coupled torsions. We have used this modified module to study the green fluorescent protein. A coupled torsional potential was adjusted on high accuracy quantum chemical calculations of the anionic chromophore in the first excited state, and several 15-ns-long MD simulations were performed. We have obtained an estimate of the fluorescence lifetime (2.2 ns) to be compared to the experimental value (3 ns), which is, to the best of our knowledge, the first theoretical estimate of that lifetime.

Free Energy Perturbation

Peptide Synthesis in Aqueous Environments: The Role of Extreme Conditions and Pyrite Mineral Surfaces on Formation and Hydrolysis of Peptides

Eduard Schreiner [Ruhr-Universitat Bochum], Nisanth N. Nair, Carsten Wittekindt, and Dominik Marx

J. Am. Chem. Soc., **133**, 8216–8226, 2011.

A comprehensive study of free energy landscapes and mechanisms of COS-mediated polymerization of glycine via N-carboxy anhydrides (NCAs, “Leuchs anhydrides”) and peptide hydrolysis at the water–pyrite interface at extreme thermodynamic conditions is presented. Particular emphasis is set on the catalytic effects of the mineral surface including the putative role of the ubiquitous sulfur vacancy defects. It is found that the mere presence of a surface is able to change the free energetics of the elementary reaction steps. This effect can be understood in terms of a reduction of entropic contributions to the reactant state by immobilizing the reactants and/or screening them from bulk water in a purely geometric (“steric”) sense.

Molecular motions in drug design: the coming age of the metadynamics method

Xevi Biarnés, Salvatore Bongarzone, Attilio Vittorio Vargiu, Paolo Carloni and Paolo Ruggerone [University of Cagliari]

J. Comp. Aided Mol. Des. **25**, 395–402, 2011.

Metadynamics is emerging as a useful free energy method in physics, chemistry and biology. Recently, it has been applied also to investigate ligand binding to biomolecules of pharmacological interest. Here, after introducing the basic idea of the method, we review applications to challenging targets for pharmaceutical intervention. We show that this methodology, especially when combined with a variety of other computational approaches such as molecular docking and/or molecular dynamics simulation, may be useful to predict structure and energetics of ligand/target complexes even when the targets lack a deep binding cavity, such as DNA and proteins undergoing fibrillation in neurodegenerative diseases.

QM and QM/MM

The Directive of the Protein: How Does Cytochrome P450 Select the Mechanism of Dopamine Formation?

Patric Schyman, Wenzhen Lai, Hui Chen, Yong Wang, and Sason Shaik [The Hebrew University of Jerusalem]

J. Am. Chem. Soc., **133**, 7977–7984, 2011.

Dopamine can be generated from tyramine via arene hydroxylation catalyzed by a cytochrome P450 enzyme (CYP2D6). Our quantum mechanical/molecular mechanical (QM/MM) results reveal the decisive impact of the protein in selecting the ‘best’ reaction mechanism. Instead of the traditional Meisenheimer-complex mechanism, the study reveals a mechanism involving an initial hydrogen atom transfer from the phenolic hydroxyl group of the tyramine to the iron-oxo of the compound I (Cpd I), followed by a ring- π radical rebound that eventually leads to dopamine by keto-enol rearrangement.

Use of a QM/MM-Based FEP Method to Evaluate the Anomalous Hydration Behavior of Simple Alkyl Amines and Amides: Application to the Design of FBPase Inhibitors for the Treatment of Type-2 Diabetes

M. Rami Reddy [University of Hyderabad], U. Chandra Singh, and Mark D. Erion

J. Am. Chem. Soc., **133**, 8059–8061, 2011.

Standard molecular mechanics (MM) force fields predict a nearly linear decrease in hydration free energy with each successive addition of a methyl group to ammonia or acetamide, whereas a nonadditive relationship is observed experimentally. Decomposing the free energies into electrostatic and van der Waals contributions and comparing the results with the corresponding free energies obtained using a conventional FEP method and a QM/MM method wherein the charges are not updated suggests that inaccuracies in the electrostatic free energies are the primary reason for the inability of the conventional FEP method to predict the experimental findings. The QM/MM-based FEP method was subsequently used to evaluate inhibitors of the diabetes drug target fructose-1,6-bisphosphatase adenosine 5'-monophosphate and 6-methylamino purine riboside 5'-monophosphate.

Acceleration of a QM/MM-QMC simulation using GPU

Yutaka Uejima, Tomoharu Terashima and Ryo Maezono [Japan Advanced Institute of Science and Technology]

J. Comp. Chem. **32**, 2264–2272, 2011.

We accelerated an ab initio molecular QMC calculation by using GPGPU. Only the bottle-neck part of the calculation is replaced by CUDA subroutine and performed on GPU. The performance on a (single core CPU + GPU) is compared with that on a (single core CPU with double precision), getting 23.6 (11.0) times faster calculations in single (double) precision treatments on GPU. The energy deviation caused by the single precision treatment was found to be within the accuracy

required in the calculation, $\sim 10^{-5}$ hartree.

Comparative or Homology Modeling

APOLLO: a quality assessment service for single and multiple protein models

Zheng Wang, Jesse Eickholt, and Jianlin Cheng [University of Missouri]

Bioinformatics, **27**, 1715-1716, 2011.

We built a web server named APOLLO, which can evaluate the absolute global and local qualities of a single protein model using machine learning methods or the global and local qualities of a pool of models using a pair-wise comparison approach. Based on our evaluations on 107 CASP9 (Critical Assessment of Techniques for Protein Structure Prediction) targets, the predicted quality scores generated from our machine learning and pair-wise methods have an average per-target correlation of 0.671 and 0.917, respectively, with the true model quality scores.

Ligand Docking

How Does a Drug Molecule Find Its Target Binding Site?

Yibing Shan, Eric T. Kim, Michael P. Eastwood, Ron O. Dror, Markus A. Seeliger, and David E. Shaw [D. E. Shaw Research, New York]

J. Am. Chem. Soc., **133**, 9181–9183, 2011.

Although the thermodynamic principles that control the binding of drug molecules to their protein targets are well understood, detailed experimental characterization of the process by which such binding occurs has proven challenging. We conducted relatively long, unguided molecular dynamics simulations in which a ligand (the cancer drug dasatinib or the kinase inhibitor PP1) was initially placed at a random location within a box that also contained a protein (Src kinase) to which that ligand was known to bind.

Comparing and combining implicit ligand sampling with multiple steered molecular dynamics to study ligand migration processes in heme proteins

Flavio Forti, Leonardo Boechi, Dario A. Estrin and Marcelo A. Marti [Facultad de Ciencias Exactas y Naturales Universidad de Buenos Aires]

J. Comp. Chem. **32**, 2219–2231, 2011.

The ubiquitous heme proteins perform a wide variety of tasks that rely on the subtle regulation of their affinity for small ligands like O₂, CO, and NO. Ligand affinity is characterized by kinetic association and dissociation rate constants, that partially depend on ligand migration between the solvent and active site, mediated by the presence of internal cavities or tunnels. Different computational methods have been developed to study these processes which can be roughly divided in two strategies: those costly methods in which the ligand is treated explicitly during the simulations, and the free energy landscape of the process is computed; and those faster methods that use prior computed Molecular Dynamics simulation without the ligand, and incorporate it afterwards, called implicit ligand sampling (ILS) methods.

Ligand Docking (Cont'd)

The effects of amino-acid mutations on specific interactions between urokinase-type plasminogen activator and its receptor: Ab initio molecular orbital calculations

Shingo Tsuji, Tomoyo Kasumi, Keisuke Nagase, Eri Yoshikawa, Hiroshi Kobayashi, Noriyuki Kurita [Toyohashi University of Technology]

J. Mol.Graph. and Mod., **29**, 975-984, 2011.

During cancer invasion, the binding of urokinase-type plasminogen activator (uPA) to its receptor (uPAR) on the surface of a cancer cell is considered a trigger for invasion. Here, we present a stable structure of the solvated complex formed between uPA and uPAR (uPA-uPAR) and investigate the specific interactions between uPA and uPAR by ab initio fragment molecular orbital (FMO) calculations. The result indicates that the electrostatic interactions between the charged amino acid residues existing in both uPA and uPAR make a large contribution to the binding between uPA and uPAR.

Structural determinants of the alpha2 adrenoceptor subtype selectivity

Liliana Ostopovici-Halip [Institute of Chemistry Timisoara], Ramona Curpăn, Maria Mracec, Cristian G. Bologa

J. Mol.Graph. and Mod., **29**, 1030-1038, 2011.

Alpha2-adrenergic receptor (α 2-AR) subtypes, acting mainly on the central nervous and cardiovascular systems, represent important targets for drug design, confirmed by the high number of studies published so far. Presently, only a few α 2-AR subtype selective compounds are known. Using homology modeling and ligand docking, the present study analyzes the similarities and differences between binding sites, and between extracellular loops of the three subtypes of α 2-ARs. The observed differences between binding site residues provide an excellent starting point for virtual screening of chemical databases, in order to identify potentially selective ligands for α 2-ARs.

The effect of electrostatics on factor H function and related pathologies

Chris A. Kieslich, Homero Vazquez, Gabrielle N. Goodman, Aliana López de Victoria, Dimitrios Morikis [University of California, Riverside]

J. Mol.Graph. and Mod., **29**, 1047-1055, 2011.

Factor H (FH) contributes to the regulation of the complement system by binding to polyanionic surfaces and the proteins C3b/C3c/C3d. This implicates charge and electrostatic interactions in recognition and binding of FH. We have implemented a computational framework for comparative analysis of the charge and electrostatic diversity of FH modules and C3b domains to identify electrostatic hotspots and predict potential binding sites. We present a model of non-specific electrostatic interactions of FH with polyanion-rich surfaces and specific interactions with C3b, using our computational data and existing experimental data.

Identification of ligand binding site on RXR γ using molecular docking and dynamics methods

Peng Zhao, Qing-hua Liao, Cheng-Feng Ren and Jing Wei [Tianjin University]

J. Mol.Mod., **17**, 1259-1265, 2011.

Retinoid X receptors (RXR α , β and γ) are recently known to be cancer chemotherapies targets. The ligand binding domains of RXRs have been crystallized, but the information of RXR γ ligand binding site is not yet available due to the lack of liganded complex. A thorough understanding of the ligand binding sites is essential to study RXRs and may result in cancer therapeutic breakthrough. Thus we aimed to study the RXR γ ligand binding site and find out the differences

between the three subtypes.

Ligand Docking (Cont'd)

Comparative analysis of receptor binding by chicken and human interleukin-1 β

Chao-Sheng Cheng, Wen-Shiang Lu, I-Fan Tu, Ping-Chiang Lyu and Hsien-Sheng Yin [National Tsing Hua University]

J. Mol.Mod., **17**, 1283-1294, 2011.

Interleukin-1 β (IL-1 β) is an important cytokine in the immune system. Mammalian and avian IL-1 β s share only 31-35% sequence identity, and the function of avian IL-1 β s is less well understood by comparison. Analysis of the structures and sequences of IL-1 β s reveals that the major differences lie in loops. Modeling docking of chicken IL-1 β to its receptor reveals that these variable loops are critical for receptor binding. Molecular dynamics simulations of the IL-1 β s reveal significant changes in the dynamic range of motion upon receptor binding.

Full and Partial Agonism of Ionotropic Glutamate Receptors Indicated by Molecular Dynamics Simulations

Pekka A. Postila, Mikko Ylilauri, and Olli T. Pentikainen [University of Jyväskylä]

J.Chem. Infor. and Mod. **51**, 1037–1047, 2011.

Ionotropic glutamate receptors (iGluRs) are synaptic proteins that facilitate signal transmission in the central nervous system. Extracellular iGluR cleft closure is linked to receptor activation; however, the mechanism underlying partial agonism is not entirely understood. Recently, we have shown that the iGluR-LBD closure stage can be recreated by inserting a ligand into the closed cleft and simulating the ligand–receptor complex with molecular dynamics. The simulation protocol presented here can be used to categorize compounds in silico as partial or full agonists for iGluRs.

Rigorous Treatment of Multispecies Multimode Ligand–Receptor Interactions in 3D-QSAR: CoMFA Analysis of Thyroxine Analogs Binding to Transthyretin

Senthil Natesan, Tiansheng Wang, Viera Lukacova, Vladimir Bartus, Akash Khandelwal, and Stefan Balaz [Vermont Campus, Colchester]

J.Chem. Infor. and Mod. **51**, 1132–1150, 2011.

For a rigorous analysis of the receptor–ligand binding, speciation of the ligands caused by ionization, tautomerism, covalent hydration, and dynamic stereoisomerism needs to be considered. Each species may bind in several orientations or conformations (modes), especially for flexible ligands and receptors. We have implemented the MS-MM correlation expression into the comparative molecular field analysis (CoMFA), which deduces a map of the binding site from structures and binding affinities of a ligand set, in the absence of experimental structural information on the receptor.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 29(8), August, 2011.

975-984 **The effects of amino-acid mutations on specific interactions between urokinase-type plasminogen activator and its receptor: Ab initio molecular orbital calculations**, Shingo Tsuji, Tomoyo Kasumi, Keisuke Nagase, Eri Yoshikawa, Hiroshi Kobayashi, Noriyuki Kurita [Toyohashi University of Technology]

See Methodology / Ligand Docking.

985-995 **In silico prediction of unbound brain-to-plasma concentration ratio using machine learning algorithms**, Hongming Chen [AstraZeneca R&D Mölndal], Susanne Winiwarter, Markus Fridén, Madeleine Antonsson, Ola Engkvist

Distribution over the blood–brain barrier (BBB) is an important parameter to consider for compounds that will be synthesized in a drug discovery project. However, recently it has been proposed that the unbound brain-to-plasma concentration ratio ($K_{p,uu,brain}$) is more relevant. In the current study, quantitative $K_{p,uu,brain}$ prediction models have been built on a set of 173 in-house compounds by using various machine learning algorithms.

996-1005 **Binding conformation prediction between human acetylcholinesterase and cytochrome c using molecular modeling methods**, Songmi Kim, Yuno Lee, Pretina Lazar, Minky Son, Ayoung Baek, Sundarapandian Thangapandian, Na Young Jeong, Young Hyun Yoo, Keun Woo Lee [Gyeongsang National University]

See Applications / Ligand Binding.

1006-1014 **Inter-ring rotation of apolipoprotein A-I protein monomers for the double-belt model using biased molecular dynamics**, Thomas R. Caulfield [Georgia Institute of Technology]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

1015-1024 **A second Ig-like domain identified in dystroglycan by molecular modelling and dynamics**, Maria Cristina De Rosa, Davide Piroli, Manuela Bozzi, Francesca Sciandra, Bruno Giardina, Andrea Brancaccio [Università Cattolica del Sacro Cuore]

See Applications / Crystal Growth.

1025-1029 **Computational modeling of a rotary nanopump**, A. Lohrasebi [University of Isfahan], Y. Jamali

See Applications / Carbon Nanotubes.

- 1030-1038 **Structural determinants of the α 2 adrenoceptor subtype selectivity**, Liliana Ostopovici-Halip [Institute of Chemistry Timisoara], Ramona Curpăn, Maria Mracec, Cristian G. Bologa

See Methodology / Ligand Docking.

- 1039-1046 **Probing the reactivation process of sarin-inhibited acetylcholinesterase with α -nucleophiles: Hydroxylamine anion is predicted to be a better antidote with DFT calculations**, Md Abdul Shafeeuulla Khan, Rabindranath Lo, Tusar Bandyopadhyay, Bishwajit Ganguly [Central Salt & Marine Chemicals Research Institute, Bhavnagar]

See Applications / Enzyme Catalysis.

- 1047-1055 **The effect of electrostatics on factor H function and related pathologies**, Chris A. Kieslich, Homero Vazquez, Gabrielle N. Goodman, Aliana López de Victoria, Dimitrios Morikis [University of California, Riverside]

See Methodology / Ligand Docking.

Journal of Computational Chemistry, 32(10), July, 2011.

- 2055–2063 **π – π interaction of quinacridone derivatives**, Zhaowei Huang, Hui Sun, Houyu Zhang, Yue Wang and Fei Li [Jilin University]

We perform theoretical studies on the molecular interaction in the dimers of QAs to illustrate π – π interactions in terms of their strength, geometrical preference, substituent effect, and physical nature.

- 2064–2076 **Electron localization and delocalization indices for solids**, Alexey I. Baranov [Max Planck Institute for Chemical Physics of Solids] and Miroslav Kohout

The electron localization and delocalization indices obtained by the integration of exchange-correlation part of pair density over chemically meaningful regions of space, e.g., QTAIM atoms are valuable tools for the bonding analysis in molecular systems. However, among periodic systems only few simplest models were analyzed with this approach until now. This contribution reports implementation and evaluation of the localization and delocalization indices on the basis of solid state DFT calculations.

- 2077–2083 **Methylation of zebularine investigated using density functional theory calculations**, Lalitha Selvam, Fang Fang Chen and Feng Wang [Swinburne University of Technology]

Deoxyribonucleic acid (DNA) methylation is an epigenetic phenomenon, which adds methyl groups into DNA. This study reveals methylation of a nucleoside antibiotic drug 1-(β -D-ribofuranosyl)-2-pyrimidinone (zebularine or zeb) with respect to its methylated analog, 1-(β -D-ribofuranosyl)-5-methyl-2-pyrimidinone (d5) using density functional theory calculations in valence electronic space.

- 2084–2096 **Calculation of free energy landscapes: A histogram reweighted metadynamics approach**, Jens Smiatek [Westfälische Wilhelms-Universität Münster] and Andreas Heuer

See Applications / Free Energy Calculations.

- 2097–2103 **Minimum MD simulation length required to achieve reliable results in free energy perturbation calculations: Case study of relative binding free energies of fructose-1,6-bisphosphatase inhibitors**, R.S. Rathore, P. Aparoy, P. Reddanna, A. K. Kondapi and M. Rami Reddy [University of Hyderabad]

See Applications / Free Energy Calculations.

- 2104–2118 **Variational transition-state theory study of the rate constant of the DMS·OH scavenging reaction by O₂**, Juan M. Ramírez-Angueta, àngels González-Lafont [Universitat Autònoma de Barcelona] and José M. Lluch

The chemical tropospheric dimethyl sulfide (DMS, CH₃SCH₃) degradation involves several steps highly dependent on the environmental conditions. The experimental observations have been explained by a two-channel mechanism consisting of a H-abstraction process leading to CH₃S(O)CH₃ and HO₂ and an addition reaction leading to the DMS·OH adduct.

- 2119–2126 **Parameterization of Org27569: An allosteric modulator of the cannabinoid CB₁ G protein-coupled receptor**, Hadley A. Iliff, Diane L. Lynch, Evangelia Kotsikorou and Patricia H. Reggio [University of North Carolina at Greensboro]

See Methodology / Potentials and Parameters.

- 2127–2139 **Dipole preserving and polarization consistent charges**, Peng Zhang, Peng Bao and Jiali Gao [University of Minnesota]

A method for estimating dipole preserving and polarization consistent (DPPC) charges is described, which reproduces exactly the molecular dipole moment as well as the local, atomic hybridization dipoles determined from the corresponding wave function and can yield accurate molecular polarization.

- 2140–2148 **Empirical prediction of protein pK_a values with residue mutation**, Steven K. Burger and Paul W. Ayers [McMaster University]

A fast, empirical method, Mut-pK_a, is presented for predicting the pK_a values of ionizable residues in proteins based on mutation.

- 2149–2159 **Fast docking using the CHARMM force field with EADock DSS**, Aurélien Grosdidier, Vincent Zoete and Olivier Michielin [Swiss Institute of Bioinformatics]

See Applications / Bioinformatics.

- 2160–2169 **Molecular dynamics simulations and free energy calculations on the enzyme 4-hydroxyphenylpyruvate dioxygenase**, Stephanie B. A. De Beer, Alice Glättli, Johannes Hutzler, Nico P. E. Vermeulen and Chris Oostenbrink [Vrije Universiteit]

See Methodology / Potentials and Parameters.

- 2170–2176 **Probing the structural and electronic effects to stabilize nonplanar forms of thioamide derivatives: A computational study**, Manoj K. Kesharwani and Bishwajit Ganguly [Central Salt and Marine Chemicals Research Institute, Bhavnagar]

Density functional calculations have been performed to examine the stability of nonplanar conformations of thioamide derivatives.

- 2177–2185 **Role of nonlocal exchange in molecular crystals: The case of two proton-ordered phases of ice**, Frédéric Labat [Chimie des Interfaces et Modélisation pour l'Energie], Claude Pouchan, Carlo Adamo and Gustavo E. Scuseria

We present a periodic density functional theory investigation of two proton-ordered phases of ice.

- 2186–2194 **How to find an optimum cluster size through topological site properties: MoS_x model clusters**, Alexander M. Silva and Itamar Borges Jr. [Instituto Militar de Engenharia]

Computational investigations in catalysis frequently use model clusters to represent realistically the catalyst and its reaction sites. An approach is suggested to study model clusters based on the distributed multipole analysis (DMA) of molecular charge properties.

- 2195–2203 **Toward robust computational electrochemical predicting the environmental fate of organic pollutants**, Liudmila Sviatenko, Olexandr Isayev, Leonid Gorb, Frances Hill and Jerzy Leszczynski [Jackson State University]

A number of density functionals was utilized for the calculation of electron attachment free energy for nitrocompounds, quinones and azacyclic compounds.

- 2204–2218 **Ensemble QSAR: A QSAR method based on conformational ensembles and metric descriptors**, Raghuvir R. S. Pissurlenkar, Vijay M. Khedkar, Radhakrishnan P. Iyer and Evans C. Coutinho [Bombay College of Pharmacy, Kalina]

See Methodology / QSAR.

- 2219–2231 **Comparing and combining implicit ligand sampling with multiple steered molecular dynamics to study ligand migration processes in heme proteins**, Flavio Forti, Leonardo Boechi, Dario A. Estrin and Marcelo A. Marti [Facultad de Ciencias Exactas y Naturales Universidad de Buenos Aires]

See Methodology / Ligand Docking.

- 2232–2244 **Automated RNA tertiary structure prediction from secondary structure and low-resolution restraints**, Matthew G. Seetin and David H. Mathews [University of Rochester Medical Center]

See Applications / Nucleic Acids.

- 2245–2253 **Efficiency of tabu-search-based conformational search algorithms**, Christoph Grebner, Johannes Becker, Svetlana Stepanenko and Bernd Engels [Institut für Physikalische und Theoretische Chemie]

See Methodology / Molecular Dynamics.

- 2254–2263 **Quantum mechanical binding free energy calculation for phosphopeptide inhibitors of the Lck SH2 domain**, Victor M. Anisimov and Claudio N. Cavasotto [University of Texas Health Science Center at Houston]

See Applications / Free Energy Calculations.

- 2264–2272 **Acceleration of a QM/MM-QMC simulation using GPU**, Yutaka Uejima, Tomoharu Terashima and Ryo Maezono [Japan Advanced Institute of Science and Technology]

See Methodology / QM and QM/MM.

- 2273–2289 **Implementation and evaluation of a docking-rescoring method using molecular footprint comparisons**, Trent E. Balius, Sudipto Mukherjee and Robert C. Rizzo [Stony Brook University]

A docking-rescoring method, based on per-residue van der Waals (VDW), electrostatic (ES), or hydrogen bond (HB) energies has been developed to aid discovery of ligands that have interaction signatures with a target (footprints) similar to that of a reference.

- 2290–2297 **Conformational state-specific free energy differences by one-step perturbation: Protein secondary structure preferences of the GROMOS 43A1 and 53A6 force fields**, Zhixiong Lin, Wilfred F. Van Gunsteren and Haiyan Liu [University of Science and Technology of China]

See Methodology / Potentials and Parameters.

- 2298–2312 **Computational study of energetic nitrogen-rich derivatives of 1,1'- and 5,5'-bridged ditetrazoles**, Weihua Zhu, Chenchen Zhang, Tao Wei and Heming Xiao [Nanjing University of Science and Technology]

Density functional theory method was used to study the heats of formation (HOFs), electronic structure, energetic properties, and thermal stability for a series of bridged ditetrazole derivatives with different linkages and substituent groups.

Journal of Computational Chemistry, 32(11), August, 2011.

- 2339–2347 **Harmonic vibrational frequencies: Scale factors for pure, hybrid, hybrid meta, and double-hybrid functionals in conjunction with correlation consistent basis sets**, Marie L. Laury, Scott E. Boesch, Ian Haken, Pankaj Sinha, Ralph A. Wheeler and Angela K. Wilson [University of North Texas]

Scale factors for (a) low ($<1000\text{ cm}^{-1}$) and high harmonic vibrational frequencies, (b) thermal contributions to enthalpy and entropy, and (c) zero-point vibrational energies have been determined for five hybrid functionals (B3P86, B3PW91, PBE1PBE, BH&HLYP, MPW1K), five pure functionals (BLYP, BPW91, PBEPBE, HCTH93, and BP86), four hybrid meta functionals (M05, M05-2X, M06, and M06-2X) and one double-hybrid functional (B2GP-PLYP) in combination with the correlation consistent basis sets.

- 2348–2358 **Molecular dynamics simulations of ionic and nonionic surfactant micelles with a generalized born implicit-solvent model**, Yuhang Wang, Jason A. Wallace, Peter H. Koenig and Jana K. Shen [University of Oklahoma]

Surfaces, Catalysts and Material Subjects.

- 2359–2368 **SwissParam: A fast force field generation tool for small organic molecules**, Vincent Zoete, Michel A. Cuendet, Aurélien Grosdidier and Olivier Michielin [Swiss Institute of Bioinformatics]

We present a fast force field generation tool, called SwissParam, able to generate, for arbitrary small organic molecule, topologies, and parameters based on the Merck molecular force field, but in a functional form that is compatible with the CHARMM force field.

- 2369–2385 **A versatile method for systematic conformational searches: Application to CheY**, Robert J. Petrella [Harvard University]

A novel molecular structure prediction method, the Z Method, is described. It provides a versatile platform for the development and use of systematic, grid-based conformational search protocols, in which statistical information (i.e., rotamers) can also be included.

- 2386–2396 **QSAR model reproducibility and applicability: A case study of rate constants of hydroxyl radical reaction models applied to polybrominated diphenyl ethers and (benzo-)triazoles**, Partha Pratim Roy, Simona Kovarich and Paola Gramatica [University of Insubria]

The crucial importance of the three central OECD principles for quantitative structure-activity relationship (QSAR) model validation is highlighted in a case study of tropospheric degradation of volatile organic compounds (VOCs) by OH, applied to two CADASTER chemical classes (PBDEs and (benzo-)triazoles).

- 2397–2403 **On the applicability of cluster models to study the chemical reactivity of carbon nanotubes**, Pablo A. Denis [Facultad de Química] and Federico Iribarne

See Applications / Carbon Nanoparticles.

- 2404–2413 **He_2^{2+} molecular ion in a strong time-dependent magnetic field: A current-density functional study**, Vikas [Panjab University]

The He_2^{2+} molecular ion exposed to a strong ultrashort time-dependent (TD) magnetic field of the order of 10^9 G is investigated through a quantum fluid dynamics (QFD) and current-density functional theory (CDFT) based approach using vector exchange-correlation (XC) potential and energy density functional that depend not only on the electronic charge-density but also on the current density.

- 2414–2421 **Computer simulation of trifluoromethane properties with ab initio force field**, Yi-Hsing Chung, Arvin Huang-Te Li and Sheng D. Chao [National Taiwan University]

Intermolecular interaction potentials of the trifluoromethane dimer in 15 orientations have been calculated using the Hartree-Fock (HF) self-consistent theory and the second-order Møller-Plesset (MP2) perturbation theory.

- 2422–2431 **A dissected ring current model for assessing magnetic aromaticity: A general approach for both organic and inorganic rings**, Cina Foroutan-Nejad, Shant Shahbazian, Ferran Feixas, Parviz Rashidi-Ranjbar and Miquel Solà [Universitat de Girona]

A model based on classical electrodynamics is used to measure the strength of ring currents of different molecular orbitals, i.e., σ - and π -orbitals, and characteristics of ring current loops, i.e., ring current radii and height of current loops above/below the ring planes, among a number of organic as well as inorganic molecules.

- 2432–2440 **The structure, properties, and nature of HArF-HOX (X = F, Cl, Br) complex: An ab initio study and an unusual short hydrogen bond**, Qing-Zhong Li [Yantai University], Jun-Ling Zhao, Bo Jing, Ran Li, Wen-Zuo Li and Jian-Bo Cheng

The structure and properties (geometric, energetic, electronic, spectroscopic, and thermodynamic properties) of HArF-HOX (X = F, Cl, Br) complex have been investigated at the MP2/aug-cc-pVTZ level.

- 2441–2448 **Application of a ligand-based theoretical approach to derive conversion paths and ligand conformations in CYP11B2-mediated aldosterone formation**, Luc Roumen, Bram Van Hoof, Koen Pieterse, Peter A.J. Hilbers, Erica M.G. Custers, Ralf Plate, Marcel De Gooyer, Ilona P.E. Beugels, Judith M.A. Emmen, Dirk Leysen, Jos F.M. Smits, Harry C.J. Ottenheijm and J.J. Rob Hermans [Eindhoven University of Technology]

See Applications / Enzyme Catalysis.

- 2449–2458 **Avoiding the van der Waals endpoint problem using serial atomic insertion**, Stefan Boresch [University of Vienna] and Stefan Bruckner

In the past analyses of the so-called van der Waals end point problem focused on thermodynamic integration. Here we investigate which of the recommendations, such as the need for soft-core potentials, are still valid when Bennett's acceptance ratio method is used.

- 2459–2473 **Point atomic multipole moments for simulation of electrostatic potential and field in all-siliceous zeolites**, Alexander V. Larin [MSU, Moscow]

Calibration method of atomic multipole moments (AMMs) is presented with respect to geometries of all-siliceous zeolite models obtained with X-ray diffraction (XRD) methods.

- 2474–2478 **Giant magnetic moment of the core-shell Co₁₃@Mn₂₀ clusters: First-principles calculations**, Qun Jing, Hai-Bin Cao, Gui-Xian Ge, Yuan Xu Wang [Henan University], Hong-Xia Yan, Zi-Ying Zhang and Yun-Hu Liu

The core-shell clusters Co₁₃@TM₂₀ with TM = Mn, Fe, Co, and Ni are investigated within first-principles simulations in the framework of density-functional theory.

- 2479-2491 **Theoretical study of valance photoelectron spectra of hypoxanthine, xanthine, and caffeine using direct symmetry-adapted cluster/configuration interaction methodology**, Hossein Farrokhpour [Isfahan University of Technology] and Fariman Fathi

UV photoelectron spectra of hypoxanthine, xanthine, and caffeine, up to 20 eV, were calculated and compared with the experimental spectra reported in literature.

Journal of Molecular Modeling, 17(6), June, 2011.

- 1227-1239 **Electronic structure and conformational properties of 1H-indole-3-acetic acid**, María C. Pérez Schmit, Alicia H. Jubert, Arturo Vitale and Rosana M. Lobayan [Universidad de la Cuenca del Plata]

The conformational space of 1H-Indole-3-Acetic Acid (IAA) was scanned using molecular dynamics at semiempirical level, and complemented with functional density calculations at B3LYP/6-31G** level, 14 conformers of lowest energy were obtained.

- 1241-1249 **Experimental and computational studies indicate the mutation of Glu12 to increase the thermostability of oligomeric protease from *Pyrococcus horikoshii***, Dongling Zhan, Weiwei Han [Jilin University] and Yan Feng

See Applications / Ligand Binding.

- 1251-1257 **Mechanistic investigation of the base-promoted cycloselenoetherification of pent-4-en-1-ol**, Marina D. Rvovic, Vera M. Divac, Ralph Puchta and Zorica M. Bugarčić [University of Kragujevac]

The mechanism of phenylselenoetherification of pent-4-en-1-ol using some bases (pyridine, triethylamine, quinoline, 2,2'-bipyridine) as catalyst was examined through studies of kinetics of the cyclization, by UV-VIS spectrophotometry.

- 1259-1265 **Identification of ligand binding site on RXR γ using molecular docking and dynamics methods**, Peng Zhao, Qing-hua Liao, Cheng-Feng Ren and Jing Wei [Tianjin University]

See Methodology / Ligand Docking.

- 1267-1272 **A MP2 and DFT study of the aromatic character of polyphosphaphospholes. Is the pyramidalty the only factor to take into consideration?**, Daniela Josa, Angeles Peña-Gallego [Universidade de Santiago de Compostela], Jesús Rodríguez-Otero and Enrique M. Cabaleiro-Lago

A comprehensive MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) study of the aromatic character of phospholes, P n (CH)4-n PH with n=0-4 was conducted.

- 1273-1281 **A PM6 study of Rhodopseudomonas Acidophila light harvesting center II B800 bacteriochlorophylls in representative protein environment**, Sina Türeli [Boğaziçi University] and Tereza Varnali

See Applications / Protein Structure Analysis.

- 1283-1294 **Comparative analysis of receptor binding by chicken and human interleukin-1 β** , Chao-Sheng Cheng, Wen-Shiang Lu, I-Fan Tu, Ping-Chiang Lyu and Hsien-Sheng Yin [National Tsing Hua University]

See Methodology / Ligand Docking.

- 1295-1309 **Aromaticity balance, π -electron cooperativity and H-bonding properties in tautomerism of salicylideneaniline: the quantum theory of atoms in molecules (QTAIM) approach**, Hasan Karabiyik [Dokuz Eylül University], Resul Sevinçek, Hande Petek and Muhittin Aygün

Topological analysis based on DFT calculations regarding proton transfer reaction in salicylideneaniline (SA) was performed to scrutinize possible changes in the intramolecular H-bond, π -electron delocalization and aromaticity levels of certain fragments.

- 1311-1315 **Aromaticity in cyanuric acid**, Liliana Pérez-Manríquez, Armando Cabrera, Luis Enrique Sansores and Roberto Salcedo [Universidad Nacional Autónoma de México]

This study analyzes the aromatic nature of cyanuric acid (hexahydrotriazine) and some of its derivatives, in terms of aromatic stabilization energy (ASE) and electronic behavior.

- 1317-1323 **Theoretical studies on sulfanilamide and derivatives with antibacterial activity: conformational and electronic analysis**, Esteban G. Vega-Hissi [Universidad Nac. de San Luis], Matías F. Andrada, Graciela N. Zamarbide, Mario R. Estrada and Francisco Tomás-Vert

Quantum chemical methods have been used to study the conformational and electronic properties of sulfanilamide and derivatives with antibacterial activity.

- 1325-1334 **Preference for bridging versus terminal ligands in magnesium dimmers**, Hadi Lioe, Jonathan M. White and Richard A. J. O'Hair [The University of Melbourne]

Magnesium dimers play important roles in inorganic and organometallic chemistry. This study evaluates the inherent bridging ability of a range of different ligands in magnesium dimmers.

- 1335-1342 **Kinetically stable high-energy isomers of C₁₄H₁₂ and C₁₂H₁₀N₂ derived from cis-stilbene and cis-azobenzene**, Jon Baker and Krzysztof Wolinski [Parallel Quantum Solutions]

Following on from our recent enforced geometry optimization (EGO) investigation of isomerization in cis-stilbene (J Comput Chem, in press) we report the discovery of two interesting new, symmetrical "fused sandwich" isomers of both cis-stilbene and the related cis-azobenzene.

- 1343-1351 **Singular value decomposition analysis of the torsional angles of dopamine reuptake inhibitor GBR 12909 analogs: effect of force field and charges**, Deepangi Pandit, Anna Fiorentino, Supreet Bindra and Carol A. Venanzi [New Jersey Institute of Technology]

See Applications / QSAR.

- 1353-1370 **Structural analysis of natural killer cell receptor protein 1 (NKR-P1) extracellular domains suggests a conserved long loop region involved in ligand specificity**, Žofie Sovová, Rüdiger Ettrich

[Academy of Sciences of the Czech Republic], Vladimír Kopecký, Tomáš Pazderka, Kateřina Hofbauerová and Daniel Rozbeský, et al

See Applications / Ligand Binding.

- 1371-1379 **Electronic structure and PCA analysis of covalent and non-covalent acetylcholinesterase inhibitors**, Érica Cristina Moreno Nascimento [Universidade de Brasília] and João B. L. Martins

Hartree-Fock and density functional methods were used to analyze electronic and structural properties of known drugs to evaluate the influence of these data on acetylcholinesterase inhibition.

- 1381-1392 **Theoretical studies and vibrational spectra of 1H-indole-3-acetic acid. Exploratory conformational analysis of dimeric species**, Rosana Maria Lobayan [Universidad de la Cuenca del Plata], María Celia Pérez Schmit, Alicia H. Jubert and Arturo Vitale

Theoretical studies on 1H-indole-3-acetic acid (IAA) were performed to investigate the conformational properties of dimeric species and vibrational spectra.

- 1393-1400 **How many hydrogen-bonded α -turns are possible?**, Anette Schreiber, Peter Schramm and Hans-Jörg Hofmann [University of Leipzig]

The formation of α -turns is a possibility to reverse the direction of peptide sequences via five amino acids. In this paper, a systematic conformational analysis was performed to find the possible isolated α -turns with a hydrogen bond between the first and fifth amino acid employing the methods of ab initio MO theory in vacuum (HF/6-31G*, B3LYP/6-311++G*) and in solution (CPCM/HF/6-31G*).

- 1401-1412 **Docking of the alkaloid geissospermine into acetylcholinesterase: a natural scaffold targeting the treatment of Alzheimer's disease**, Jocley Queiroz Araújo [Universidade Federal do Rio de Janeiro], Josélia Alencar Lima, Angelo da Cunha Pinto, Ricardo Bicca de Alencastro and Magaly Girão Albuquerque

See Applications / Ligand Binding.

- 1413-1425 **A comparative study of one- and two-photon absorption properties of pyrene and perylene diimide derivatives**, Xiao-Ting Liu, Yang Zhao, Ai-Min Ren [Jilin University] and Ji-Kang Feng

Two important classes of organic molecules, perylene diimide (PDI) and pyrene derivatives have been found to possess relatively excellent photophysical and photochemical properties and especially high two-photon absorption cross sections ($\delta T_{\max}$). Herein, one-photon absorption (OPA) and two-photon absorption (TPA) properties of some novel PDI and pyrene derivatives were comparatively investigated by the density functional theory (DFT) and Zerner's intermediate neglect of differential overlap (ZINDO) methods.

- 1427-1433 **Sigma- and pi- electron structure of aza-azoles**, Tadeusz M. Krygowski, Wojciech P. Oziminski [National Medicines Institute, Chelmska] and Christopher A. Ramsden

The reasons behind changes of aromaticity in 10 unsubstituted aza-azoles were analysed by employing the natural bond orbital (NBO) approach at the MP2/6-311+G(d,p) level of theory.

- 1435-1444 **Hybridization-displaced charges for amino-acids: a new model using two point charges per atom along with bond-center charges**, Neha Agnihotri and P. C. Mishra [Banaras Hindu University]

A new charge distribution is proposed for the amino acids where each atom is associated with two point charges while each bond center is associated with one point charge.

- 1445-1456 **The binding properties of the H5N1 influenza virus neuraminidase as inferred from molecular modeling**, Michal Raab and Igor Tvaroška [Slovak Academy of Sciences]

See Applications / Ligand Binding.

- 1457-1465 **Molecular dynamics study of solvation effect on diffusivity changes of DNA fragments**, Kentaro Doi [Osaka University], Takamasa Uemura and Satoyuki Kawano

See Applications / nucleic Acids.

- 1467-1472 **Arginine interactions with anatase TiO₂ (100) surface and the perturbation of ⁴⁹Ti NMR chemical shifts – a DFT investigation: relevance to Renu-Seeram bio solar cell**, Rainer Koch [University of Oldenburg], Andrew S. Lipton, Slawomir Filipek and Venkatesan Renugopalakrishnan

Density functional theoretical calculations have been utilized to investigate the interaction of the amino acid arginine with the (100) surface of anatase and the reproduction of experimentally measured ⁴⁹Ti NMR chemical shifts of anatase.

- 1473-1482 **Integrating computational and mixture-based screening of combinatorial libraries**, Austin B. Yongye, Clemencia Pinilla, Karina Martínez-Mayorga [Torrey Pines Institute for Molecular Studies], Jose L. Medina-Franco, Marc A. Giulianotti and Colette T. Dooley, et al.

See Applications / Bioinformatics.

- 1483-1492 **Rational questing for potential novel inhibitors of FabK from Streptococcus pneumoniae by combining FMO calculation, CoMFA 3D-QSAR modeling and virtual screening**, Qingye Zhang, Chan Yu, Jun Min, Ziniu Yu [Huazhong Agricultural University], Yan Wang and Jin He, et al.

See Applications / Medicinal Chemmistry and Drug Design.

- 1493-1506 **Simulation on the structure of pig liver esterase**, Daniel Hasenpusch, Uwe T. Bornscheuer and Walter Langel [University of Greifswald]

See Applications / Homology Modeling.

- 1507-1515 **Theoretical studies on nitrogen rich energetic azoles**, Vikas Dasharath Ghule [University of Hyderabad], Radhakrishnan Sarangapani, Pandurang M. Jadhav and Surya P. Tewari

Different nitro azole isomers based on five membered heterocyclics were designed and investigated using computational techniques in order to find out the comprehensive relationships between structure and performances of these high nitrogen compounds.

- 1517-1524 **Calculation of multicenter electric field gradient integrals over Slater-type orbitals using unsymmetrical one-range addition theorems**, Israfil I. Guseinov and Nurşen Seçkin Görgün [Trakya University]

The electric field induced within a molecule by its electrons determines a whole series of important physical properties of the molecule. Using unsymmetrical one-range addition theorems introduced by one of the authors, the sets of series expansion relations for multicenter electric field gradient integrals over Slater-type orbitals in terms of multicenter charge density expansion coefficients and two-center basic integrals are presented. The convergence of the series is tested by calculating concrete cases for different values of quantum numbers, parameters and locations of orbitals.

- 1525-1528 **On the molecular mechanisms of the acid-induced dissociation of hydroxy-apatite in water**, Oliver Hochrein and Dirk Zahn [Friedrich-Alexander Universität Erlangen-Nürnberg]

The enamel/saliva interface is mimicked by the comparably much simpler model of (001) surfaces of hydroxy-apatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) in contact with aqueous solution.

4. ADDRESSES OF PRINCIPAL AUTHORS

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1 APPLICATIONS (90) Page 2

1.1 Small Molecules (23)

General and Model Systems	Page 2	Med. Chem. And Drug	Page 3
Water and Solvation	Page 3	QSAR	Page 7

1.2 Biopolymers (67)

Bioinformatics and Cheminformatics	Page 8	Ligand Binding	Page 17
Protein Secondary Structure	Page 9	Enzyme Catalysis	Page 18
Comparative or Homology Modeling	Page 9	Protein-Protein Interactions	Page 20
Peptide Conformational Analysis	Page 11	Membrane Proteins	Page 21
Protein Structure Analysis	Page 12	Protein Folding	Page 23
Protein Dynamics	Page 12	Protein-Nucleic Acids	Page 24
Free Energy Calculations	Page 16	Nucleic Acids	Page 25

1.3 Polymers

1.4 Surfaces, Catalysts and Material Page

2 METHODOLOGY (27) Page 26

QSAR	Page 26	QM & QM/MM	Page 29
Potentials and Parameters	Page 27	Comparative or Homology	Page 30
Molecular Dynamics	Page 27	Ligand Docking	Page 32

3 JOURNAL REVIEWS (4) Page 34

Journal of Computational Chemistry, 32 (12), September, 2011.
 Journal of Computational Chemistry, 32 (13), October, 2011.
 Journal of Molecular Modeling, 17 (7), July, 2011.
 Journal of Molecular Modeling, 17 (8), August, 2011.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 48

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Surveying implicit solvent models for estimating small molecule absolute hydration free energies

Jennifer L. Knight and Charles L. Brooks III [University of Michigan]

J. Comp. Chem. **32**, 2909–2923, 2011.

Implicit solvent models are powerful tools in accounting for the aqueous environment at a fraction of the computational expense of explicit solvent representations. Here, we compare the ability of common implicit solvent models (TC, OBC, OBC2, GBMV, GBMV2, GBSW, GBSW/MS, GBSW/MS2 and FACTS) to reproduce experimental absolute hydration free energies for a series of 499 small neutral molecules that are modeled using AMBER/GAFF parameters and AM1-BCC charges.

A tool for the morphological analysis of mixtures of lipids and water in computer simulations

Marc Fuhrmans [University of Groningen] and Siewert-Jan Marrink

J. Mol.Mod., **17**, 1755-1766, 2011.

When analyzing computer simulations of mixtures of lipids and water, the questions to be answered are often of a morphological nature. They can deal with global properties, like the kind of phase that is adopted or the presence or absence of certain key features like a pore or stalk, or with local properties, like the local curvature present at a particular part of the lipid/water interface. Here we present a tool that employs the technique of morphological image analysis (MIA) to automatically extract the global morphology—as given by Minkowski functionals—from a set of atomic coordinates, and creates an image of the system onto which the local curvatures are mapped as a color code.



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Water and Solvation

The Orientation and Charge of Water at the Hydrophobic Oil Droplet–Water Interface

Robert Vacha, Steven W. Rick, Pavel Jungwirth, Alex G. F. de Beer, Hilton B. de Aguiar, Jean-Sebastien Samson, and Sylvie Roke [Ecole Polytechnique Federale de Lausanne (EPFL)]

J. Am. Chem. Soc., **133**, 10204–10210, 2011.

We established the charge and structure of the oil/water interface by combining ζ -potential measurements, sum frequency scattering (SFS) and molecular dynamics simulations. The SFS experiments show that the orientation of water molecules can be followed on the oil droplet/water interface. The average water orientation on a neat oil droplet/water interface is the same as the water orientation on a negatively charged interface. pH dependent experiments show, however, that there is no sign of selective adsorption of hydroxide ions.

Water order profiles on phospholipid/cholesterol membrane bilayer surfaces

David Robinson, Nicholas A. Besley, Paul O'shea and Jonathan D. Hirst [University of Nottingham]

J. Comp. Chem. **32**, 2613–2618, 2011.

Water is pivotal in the stabilization of macromolecular biological structures, although the dynamic ensemble structure of water near to molecular surfaces has yet to be fully understood. We show, through molecular simulation and fluorescence measurements, that water at the membrane surface is substantially more ordered than bulk water, due to a loss of hydrogen bonding between water molecules, coupled with an alignment of lipid and water dipole moments.

Medicinal Chemistry and Drug Design

Synthesis, structural elucidation, DNA-PK inhibition, homology modelling and anti-platelet activity of morpholino-substituted-1,3-naphth-oxazines

Saleh Ihmaid [La Trobe University], Jasim Al-Rawi, Christopher Bradley, Michael J. Angove, Murray N. Robertson, Rachel L. Clark

Bioorg. and Med.Chem., **19**, 3983-3994, 2011.

A number of new angular 2-morpholino-(substituted)-naphth-1,3-oxazines (compound 10b), linear 2-morpholino-(substituted)-naphth-1,3-oxazines (compounds 13b–c), linear 6, 7 and 9-O-substituted-2-morpholino-(substituted)-naphth-1,3-oxazines (compounds 17–22, 24, and 25) and angular compounds 14–16 and 23 were synthesised. Furthermore, the compounds were also assayed for their ability to inhibit DNA-dependent protein kinase (DNA-PK) activity. The most active compounds were 18 IC₅₀ = 0.091 μ M, 24 IC₅₀ = 0.191 μ M, and 22 IC₅₀ = 0.331 μ M.

Ligand-based modelling followed by synthetic exploration unveil novel glycogen phosphorylase inhibitory leads

Maha Habash, Mutasem O. Taha [University of Jordan]

Bioorg. and Med.Chem., **19**, 4746-4771, 2011.

Glycogen phosphorylase (GP) is a valid anti-diabetic target. Accordingly, we applied a drug discovery workflow to unveil novel inhibitory GP leads via combining pharmacophore modeling, QSAR analysis and in silico screening, followed by synthetic exploration of active hits. Virtual screening identified six low micromolar inhibitory leads from the National Cancer Institute (NCI) list of compounds. The most potent hits exhibited anti-GP IC₅₀ values of 3.2 and 4.1 μ M. Synthetic exploration of hit 59 (IC₅₀ = 4.1 μ M) yielded 25 lead inhibitors with the best illustrating IC₅₀ of 3.0 μ M.

Medicinal Chemistry and Drug Design (Cont'd)

3,4,5-Trisubstituted-1,2,4-4H-triazoles as WT and Y188L mutant HIV-1 non-nucleoside reverse transcriptase inhibitors: docking-based CoMFA and CoMSIA analyses

Elena Cichero [Università degli Studi di Genova], Laura Buffa and Paola Fossa

J. Mol.Mod., **17**, 1537-1550, 2011.

3,4,5-Trisubstituted-1,2,4-4H-triazoles (TTs) have recently been identified as a new class of potent non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors. Two series of triazoles have been studied, one of which was also screened against the Y188L mutant. A computational strategy based on molecular docking studies followed by CoMFA and CoMSIA has been used to elucidate the atomic details of the RT/TT interactions and to identify the most important features impacting the TT antiretroviral activity.

Understanding the structure-activity relationship of betulinic acid derivatives as anti-HIV-1 agents by using 3D-QSAR and docking

Ping Lan, Wan-Na Chen, Zhi-Jian Huang, Ping-Hua Sun and Wei-Min Chen [Jinan University]

J. Mol.Mod., **17**, 1643-1659, 2011.

Novel anti-HIV-1 agents derived from betulinic acid have been greatly concerned. 3D-QSAR and molecular docking studies were applied to rationalize the structural requirements responsible for the anti-HIV activity of these compounds. The CoMFA and CoMSIA models resulted from 28 molecules gave r^2 values of 0.599 and 0.630, r^2 values of 0.994 and 0.958, respectively. To estimate the predictive ability of the 3D-QSAR model, an external validation was employed. Based on the contour maps generated from both CoMFA and CoMSIA, we have identified some key features in the betulinic acid derivatives that are responsible for the anti-HIV activity.

Docking and molecular dynamics study on the inhibitory activity of N, N-disubstituted-trifluoro-3-amino-2-propanols-based inhibitors of cholesteryl ester transfer protein

Bo-Liang Dong, Qing-Hua Liao and Jing Wei [Tianjin University]

J. Mol.Mod., **17**, 1727-1734, 2011.

Extensive studies suggest direct links between cholesteryl ester transfer protein (CETP), high-density lipoproteins-cholesterol level and cardiovascular diseases. Many therapeutic approaches are aimed at the CETP. A series of N, N-disubstituted-trifluoro-3-amino-2-propanol analogues are among the most highly potent and selective inhibitors of CETP described to date. For in-depth investigation into the structural and chemical features responsible for exploring the binding pocket of these compounds, as well as for the binding recognition mechanism concerned, we performed a series of automated molecular docking operations.

A computational study of CYP3A4 mediated drug interaction profiles for anti-HIV drugs

Jayakanthan Mannu, Pranitha Jenardhanan and Premendu P. Mathur [Pondicherry University]

J. Mol.Mod., **17**, 1847-1854, 2011.

Molecular docking is a reliable method with which to identify the binding conformations of substrates, inducers and inhibitors of cytochrome P450 (CYP) enzymes. We used the docking method to explore possible binding modes of an entry inhibitor (maraviroc) and non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz and etravirine) to cytochrome P450 3A4 (CYP3A4). In addition, docking results were compared with the binding conformations of HIV protease drugs to infer the binding site residues and potential drug-drug interaction profiles for combination therapy in the treatment of AIDS.

Medicinal Chemistry and Drug Design (Cont'd)

Integrating molecular docking, DFT and CoMFA/CoMSIA approaches for a series of naphthoquinone fused cyclic α -aminophosphonates that act as novel topoisomerase II inhibitors

Yi Ma, Jian-Guo Wang [Nankai University], Bin Wang and Zheng-Ming Li

J. Mol. Mod., **17**, 1899-1909, 2011.

Since they are potential topoisomerase II inhibitors, naphthoquinone fused cyclic α -aminophosphonates display anticancer activity. To explore the inhibitory mechanisms of these compounds, they were docked into the active site of Topo II structure, which allowed their probable binding modes to be predicted. Some meaningful results concerning their structure-activity relationships were obtained from DFT calculations. Models based on quantitative comparative molecular field analysis and comparative molecular similarity index analysis were derived for the steric, electrostatic, hydrophobic and H-bonding features of the compounds.

Comparison of Virtual High-Throughput Screening Methods for the Identification of Phosphodiesterase-5 Inhibitors

Sanna P. Niinivehmas, Salla I. Virtanen, Jukka V. Lehtonen, Pekka A. Postila, and Olli T. Pentikainen [University of Jyväskylä]

J. Chem. Infor. and Mod. **51**, 1353–1363, 2011.

Reliable and effective virtual high-throughput screening (vHTS) methods are desperately needed to minimize the expenses involved in drug discovery projects. Here, we present an improvement to the negative image-based (NIB) screening: the shape, the electrostatics, and the solvation state of the target protein's ligand-binding site are included into the vHTS. The results show that docking produces very good early enrichment for phosphodiesterase-5 (PDE-5); however, in general, the NIB and the ligand-based screening performed better with or without the added electrostatics.

Discovery of Novel Pim-1 Kinase Inhibitors by a Hierarchical Multistage Virtual Screening Approach Based on SVM Model, Pharmacophore, and Molecular Docking

Ji-Xia Ren, Lin-Li Li, Ren-Lin Zheng, Huan-Zhang Xie, Zhi-Xing Cao, Shan Feng, You-Li Pan, Xin Chen, Yu-Quan Wei, and Sheng-Yong Yang [Sichuan University]

J. Chem. Infor. and Mod. **51**, 1364–1375, 2011.

In this investigation, we describe the discovery of novel potent Pim-1 inhibitors by employing a proposed hierarchical multistage virtual screening (VS) approach, which is based on support vector machine-based (SVM-based VS or SB-VS), pharmacophore-based VS (PB-VS), and docking-based VS (DB-VS) methods. In this approach, the three VS methods are applied in an increasing order of complexity so that the first filter (SB-VS) is fast and simple, while successive ones (PB-VS and DB-VS) are more time-consuming but are applied only to a small subset of the entire database.

Inhibitors of SARS-3CLpro: Virtual Screening, Biological Evaluation, and Molecular Dynamics Simulation Studies

Prasenjit Mukherjee, Falgun Shah, Prashant Desai, and Mitchell Avery [University of Mississippi]

J. Chem. Infor. and Mod. **51**, 1376–1392, 2011.

SARS-CoV from the coronaviridae family has been identified as the etiological agent of Severe Acute Respiratory Syndrome (SARS), a highly contagious upper respiratory disease that reached epidemic status in 2002. SARS-3CLpro, a cysteine protease indispensable to the viral life cycle, has been identified as one of the key therapeutic targets against SARS. A combined ligand and structure-based virtual screening was carried out against the Asinex Platinum collection. Multiple low micromolar inhibitors of the enzyme were identified through this search, one of which also showed activity against SARS-CoV in a whole cell CPE assay.

Medicinal Chemistry and Drug Design (Cont'd)

A New Protocol for Predicting Novel GSK-3 β ATP Competitive Inhibitors

Jiansong Fang, Dane Huang, Wenxia Zhao, Hu Ge, Hai-Bin Luo, and Jun Xu [Sun Yat-Sen University]

J.Chem. Infor. and Mod. **51**, 1431–1438, 2011.

Glycogen synthase kinase 3 β (GSK-3 β) is a potential therapeutic target for cancer, type-2 diabetes, and Alzheimer's disease. This paper proposes a new lead identification protocol that predicts new GSK-3 β ATP competitive inhibitors with topologically diverse scaffolds. First, 3D QSAR models were built and validated. These models are based upon known GSK-3 β inhibitors, benzofuran-3-yl-(indol-3-yl) maleimides, by means of comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Second, 28 826 maleimide derivatives were selected from the PubChem database.

Novel Inhibitors of Trihydroxynaphthalene Reductase with Antifungal Activity Identified by Ligand-Based and Structure-Based Virtual Screening

Mojca Brunskole Svegelj, Samo Turk, Boris Brus, Tea Lanisnik Rizner, Jure Stojan, and Stanislav Gobec [University of Ljubljana]

J.Chem. Infor. and Mod. **51**, 1716–1724, 2011.

Curvularia lunata is a dark pigmented fungus that is the causative agent of several diseases in plants and in both immunodeficient and immunocompetent patients. 1,8-Dihydroxynaphthalene-melanin is found in the cell wall of *C. lunata* and is believed to be the important virulence factor of dematiaceous fungi. Trihydroxynaphthalene reductase is an enzyme of the 1,8-dihydroxynaphthalene-melanin biosynthetic pathway, and it thus represents an emerging target for the development of novel fungicides and antimycotics. In the present study, we describe novel inhibitors of trihydroxynaphthalene reductase from *C. lunata*.

iScreen: world's first cloud-computing web server for virtual screening and de novo drug design based on TCM database@Taiwan

Tsung-Ying Tsai, Kai-Wei Chang and Calvin Yu-Chian Chen [China Medical University]

J. Comp. Aided Mol. Des. **25**, 525-531, 2011.

The rapidly advancing researches on traditional Chinese medicine (TCM) have greatly intrigued pharmaceutical industries worldwide. To take initiative in the next generation of drug development, we constructed a cloud-computing system for TCM intelligent screening system (iScreen) based on TCM Database@Taiwan. iScreen is compacted web server for TCM docking and followed by customized de novo drug design. We further implemented a protein preparation tool that both extract protein of interest from a raw input file and estimate the size of ligand bind site.

Quantitative Structure-Activity Relations

QSAR study on angiotensin-converting enzyme inhibitor oligopeptides based on a novel set of sequence information descriptors

Xiaoyu Wang, Juan Wang, Zhihua Lin [Chongqing University of Technology], Yong Lin, Yuan Ding and Yuanqiang Wang, et al.

J. Mol.Mod., **17**, 1599-1606, 2011.

A novel set of descriptors G-scale was derived from 457 physicochemical properties of the natural amino acids. The descriptors were then applied to study on quantitative structure-activity relationships (QSARs) of nine peptide datasets of angiotensin-converting enzyme inhibitor (ACE-inhibitor) oligopeptides (between dipeptides and decapeptides) by using partial least square (PLS) regression. The multiple correlation coefficients (R²) and leave one out cross validation values (Q²) of PLS models are better than or close to the results of references.

Anti-tubercular drug designing by structure based screening of combinatorial libraries

Payel Ghosh and Manish C. Bagchi [Indian Institute of Chemical Biology]

J. Mol.Mod., **17**, 1607-1620, 2011.

In the current study, the applicability and scope of descriptor based QSAR models to complement virtual screening using molecular docking approach have been applied to identify potential virtual screening hits targeting DNA gyrase A from Mycobacterium tuberculosis, an effective and validated anti-mycobacterial target. Initially QSAR models were developed against M. fortuitum and M. smegmatis using a series of structurally related fluoroquinolone derivatives as DNA gyrase inhibitors. Both the QSAR models yielded significant cross validated Q(2) values of 0.6715 and 0.6944 and R(2) values of 0.7250 and 0.7420, respectively.

Theoretical study on modeling and prediction of optical rotation for biodegradable polymers containing α -amino acids using QSAR approaches

Shadpour Mallakpour [Isfahan University of Technology], Mehdi Hatami and Hassan Golmohammadi

J. Mol.Mod., **17**, 1743-1753, 2011.

The main purpose of the present study was modeling and prediction of the optical rotation ([M]D) of some biodegradable polymers containing α -amino acids using quantitative structure-activity relationship (QSAR) approaches. In order to attain this goal, the optical rotation of a collection of 53 polymers was selected as a data set. The data set was randomly divided into three sections, training, test and external validation sets. By using dragon software, various descriptors were calculated for all molecules in the data set.

Identification of novel 5-hydroxy-1H-indole-3-carboxylates with anti-HBV activities based on 3D QSAR studies

Hui-fang Chai [Guiyang College of Traditional Chinese Medicine], Xin-xia Liang, Lin Li, Chun-shen Zhao and Ping Gong, et al.

J. Mol.Mod., **17**, 1831-1840, 2011.

Infection with hepatitis B virus (HBV) is a major cause of liver diseases such as cirrhosis and hepatocellular carcinoma. In our previous studies, we identified indole derivatives that have anti-HBV activities. In this study, we optimize a series of 5-hydroxy-1H-indole-3-carboxylates, which exhibited potent anti-HBV activities, using three-dimensional quantitative structure-activity relationship (3D QSAR) studies with comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA).

Quantitative Structure-Activity Relations (Cont'd)

Three-dimensional quantitative structure-activity relationships of pyrrolopyridinone as cell division cycle kinase inhibitors by CoMFA and CoMSIA

Junxia Zheng, Gaokeng Xiao, Jialiang Guo, Pinghua Sun [Jinan University], Longyi Rao and Wei Chao, et al.

J. Mol. Mod., **17**, 2113-2130, 2011.

Seventy-five 1,5,6,7-tetrahydro-pyrrolo[3,2-C]pyridinone derivatives displaying potent activities against Cdc7 kinase were selected to establish 3D-QSAR models using CoMFA and CoMSIA methods. Internal and external cross-validation techniques were investigated as well as some measures including region focusing, progressive scrambling, bootstrapping and leave-group-out. The satisfactory CoMFA model predicted a q^2 value of 0.836 and an r^2 value of 0.950, indicating that electrostatic and steric properties play a significant role in potency.

A comparison of different QSAR approaches to modeling CYP450 1A2 inhibition

Sergii Novotarskyi, Iurii Sushko, Robert Korner, Anil Kumar Pandey, and Igor V. Tetko [eADMET GmbH]

J. Chem. Infor. and Mod. **51**, 1271–1280, 2011.

Prediction of CYP450 inhibition activity of small molecules poses an important task due to high risk of drug–drug interactions. CYP1A2 is an important member of CYP450 superfamily and accounts for 15% of total CYP450 presence in human liver. This article compares 80 in-silico QSAR models that were created by following the same procedure with different combinations of descriptors and machine learning methods. The training and test sets consist of 3745 and 3741 inhibitors and noninhibitors from PubChem BioAssay database.

1.2. Biopolymers

Bioinformatics and Cheminformatics

LocaPep: Localization of Epitopes on Protein Surfaces Using Peptides from Phage Display Libraries

Luis F. Pacios [Universidad Polit cnica de Madrid], Leticia Tordesillas, Arantxa Palacin, Rosa Sanchez-Monge, Gabriel Salcedo, and Araceli D az-Perales

J. Chem. Infor. and Mod. **51**, 1465–1473, 2011.

The use of peptides from a phage display library selected by binding to a given antibody is a widespread technique to probe epitopes of antigenic proteins. However, the identification of interaction sites mimicked by these peptides on the antigen surface is a difficult task. LocaPep is a computer program developed to localize epitopes using a new clusters algorithm that focuses on protein surface properties. The program is constructed with the aim of providing a flexible computational tool for predicting the location of epitopes on protein structures.

Bioinformatics and Cheminformatics (Cont'd)

PocketAlign A Novel Algorithm for Aligning Binding Sites in Protein Structures

Kalidas Yeturu and Nagasuma Chandra [Indian Institute of Science]

J.Chem. Infor. and Mod. **51**, 1725–1736, 2011.

A fundamental task in bioinformatics involves a transfer of knowledge from one protein molecule onto another by way of recognizing similarities. Such similarities are obtained at different levels, that of sequence, whole fold, or important substructures. Comparison of binding sites is important to understand functional similarities among the proteins and also to understand drug cross-reactivities. Here, we report the development of a new algorithm, PocketAlign, for obtaining structural superpositions of binding sites. The software is available as a web-service at <http://proline.physics.iisc.ernet.in/pocketalign/>.

Protein Secondary Structure

Atomic-Level Study of Adsorption, Conformational Change, and Dimerization of an α -Helical Peptide at Graphene Surface

Luchun Ou, Yin Luo, and Guanghong Wei [Fudan University]

J. Phys. Chem. B., **115**, 9813–9822, 2011.

Recent circular dichroism spectroscopy and scanning tunneling microscopy study reported that a de novo designed α -helical peptide (with amino acid sequence DELERRIRELEARIK) would transform to β -sheet structure as well as random coil structure upon the addition of graphite particles to the peptide solution and aggregate into ordered β -sheet-rich assemblies at the graphite surface. In this study, we have investigated the conformational dynamics of two chains of the α -helical peptide in the absence and presence of a graphene sheet by performing all-atom molecular dynamic simulations in explicit solvent at 310 and 330 K.

Comparative or Homology Modeling

Gaia: automated quality assessment of protein structure models

Pradeep Kota, Feng Ding, Srinivas Ramachandran, and Nikolay V. Dokholyan [University of North Carolina at Chapel Hill]

Bioinformatics. **27**, 2209–2215, 2011.

Increasing use of structural modeling for understanding structure–function relationships in proteins has led to the need to ensure that the protein models being used are of acceptable quality. Quality of a given protein structure can be assessed by comparing various intrinsic structural properties of the protein to those observed in high-resolution protein structures. In this study, we present tools to compare a given structure to high-resolution crystal structures. We assess packing by calculating the total void volume, the percentage of unsatisfied hydrogen bonds, the number of steric clashes and the scaling of the accessible surface area.

Comparative or Homology Modeling (Cont'd)

Multiple templates-based homology modeling enhances structure quality of AT1 receptor: validation by molecular dynamics and antagonist docking

Pandian Sokkar, Shylajanaciyar Mohandass and Murugesan Ramachandran [Madurai Kamaraj University]

J. Mol.Mod., **17**, 1565-1577, 2011.

We present a comparative account on 3D-structures of human type-1 receptor (AT1) for angiotensin II (AngII), modeled using three different methodologies. AngII activates a wide spectrum of signaling responses via the AT1 receptor that mediates physiological control of blood pressure and diverse pathological actions in cardiovascular, renal, and other cell types. Availability of 3D-model of AT1 receptor would significantly enhance the development of new drugs for cardiovascular diseases. Three models were generated for AT1 receptor by, (1) homology modeling with bovine rhodopsin as template, (2) homology modeling with multiple templates and (3) threading using I-TASSER web server.

Molecular dynamics studies of human receptor molecule in hemagglutinin of 1918 and 2009 H1N1 influenza viruses

Angelina Noviani Lee, Yossa Dwi Hartono, Tiedong Sun, Dawei Zhang [Nanyang Technological University], Min Li Leow and Xue-wei Liu, et al.

J. Mol.Mod., **17**, 1635-1641, 2011.

Molecular dynamics (MD) simulations were carried out to study the behavior of human receptor molecule in the hemagglutinin (HA) of 1918 and 2009 H1N1 influenza viruses respectively. The 2009 HA model was obtained by virtually mutating the 1918 HA crystal structure based on A/Mexico City/MCIG01/2009(H1N1) segment 4 sequence. We found that human receptor molecule has no binding preference between the 2009 HA and the 1918 HA. We also found that the mutated residues contribute to a more favorable binding of hemagglutinin to the human receptor molecule.

Computational Evidence for the Role of Arabidopsis thaliana UVR8 as UV-B Photoreceptor and Identification of Its Chromophore Amino Acids

Min Wu, Elin Grahn, Leif A. Eriksson, and Åke Strid [Orebro University]

J.Chem. Infor. and Mod. **51**, 1287–1295, 2011.

A homology model of the Arabidopsis thaliana UV resistance locus 8 (UVR8) protein is presented herein, showing a seven-bladed β -propeller conformation similar to the globular structure of RCC1. The UVR8 amino acid sequence contains a very high amount of conserved tryptophans, and the homology model shows that seven of these tryptophans cluster at the 'top surface' of the UVR8 protein where they are intermixed with positive residues (mainly arginines) and a couple of tyrosines.

Peptide Conformational Analysis

Conformational Coupling of the Nucleotide-Binding and the Transmembrane Domains in ABC Transporters

Po-Chao Wen, Emad Tajkhorshid [University of Illinois at Urbana-Champaign]

Biophysical Journal. **100**, 680-690, 2011.

Basic architecture of ABC transporters includes two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs). Although the transport process takes place in the TMDs, which provide the substrate translocation pathway across the cell membrane and control its accessibility between the two sides of the membrane, the energy required for the process is provided by conformational changes induced in the NBDs by binding and hydrolysis of ATP. Nucleotide-dependent conformational changes in the NBDs, therefore, need to be coupled to structural changes in the TMDs. Using MD simulations, we have investigated the structural elements involved in the conformational coupling between the NBDs and the TMDs in the *Escherichia coli* maltose transporter.

A Normal Mode-Based Geometric Simulation Approach for Exploring Biologically Relevant Conformational Transitions in Proteins

Aqeel Ahmed, Friedrich Rippmann, Gerhard Barnickel, and Holger Gohlke [Heinrich Heine University]

J.Chem. Infor. and Mod. **51**, 1604–1622, 2011.

A three-step approach for multiscale modeling of protein conformational changes is presented that incorporates information about preferred directions of protein motions into a geometric simulation algorithm. The first two steps are based on a rigid cluster normal-mode analysis (RCNMA). Low-frequency normal modes are used in the third step (NMSim) to extend the recently introduced idea of constrained geometric simulations of diffusive motions in proteins by biasing backbone motions of the protein, whereas side-chain motions are biased toward favorable rotamer states.

Refinement of protein termini in template-based modeling using conformational space annealing

Hahnbeom Park, Junsu Ko, Keehyoung Joo, Julian Lee, Chaok Seok [Seoul National University] and Jooyoung Lee

Proteins: Stru. Fun. and Bioinfo. **79**, 2725–2734, 2011.

The rapid increase in the number of experimentally determined protein structures in recent years enables us to obtain more reliable protein tertiary structure models than ever by template-based modeling. However, refinement of template-based models beyond the limit available from the best templates is still needed for understanding protein function in atomic detail. In this work, we develop a new method for protein terminus modeling that can be applied to refinement of models with unreliable terminus structures. The energy function for terminus modeling consists of both physics-based and knowledge-based potential terms with carefully optimized relative weights.

Protein Structure Analysis

New Insight into the IR-Spectra/Structure Relationship in Amyloid Fibrils: A Theoretical Study on a Prion Peptide

Laura Zanetti Polzi, Andrea Amadei, Massimiliano Aschi, and Isabella Daidone [University of L'Aquila]

J. Am. Chem. Soc., **133**, 11414–11417, 2011.

Molecular-level structural information on amyloid aggregates is of great importance for the understanding of protein-misfolding-related diseases. Nevertheless, this kind of information is experimentally difficult to obtain. In this work, we used molecular dynamics (MD) simulations combined with a mixed quantum mechanics/molecular mechanics theoretical methodology, the perturbed matrix method (PMM), in order to study the amide I' IR spectrum of fibrils formed by a short peptide, the H1 peptide, derived from residues 109 through 122 of the Syrian hamster prion protein.

Quantitative symmetry and chirality—A fast computational algorithm for large structures: Proteins, macromolecules, nanotubes, and unit cells

Chaim Dryzun, Amir Zait and David Avnir [The Hebrew University of Jerusalem]

J. Comp. Chem. **32**, 2526–2538, 2011.

Symmetry is one of the most fundamental properties of nature and is used to understand and investigate physical properties. Classically, symmetry is treated as a binary qualitative property, although other physical properties are quantitative. Using the continuous symmetry measure (CSM) methodology one can quantify symmetry and correlate it quantitatively to physical, chemical, and biological properties. In this article, we present a new method for calculating the CSM and the related continuous chirality measure (CCM) for large systems.

Protein Dynamics

A Direct Coupling between Global and Internal Motions in a Single Domain Protein? MD Investigation of Extreme Scenarios

Mehdi Bagheri Hamaneh, Liqun Zhang, Matthias Buck [Case Western Reserve University]

Biophysical Journal. **100**, 196-204, 2011.

Proteins are not rigid molecules, but exhibit internal motions on timescales ranging from femto- to milliseconds and beyond. In solution, proteins also experience global translational and rotational motions, sometimes on timescales comparable to those of the internal fluctuations. Here, we present molecular dynamics simulations of extreme case scenarios to examine whether a possible relationship exists. In our model protein, a ubiquitin-like RhoGTPase binding domain of plexin-B1, we removed either internal or global motions.

The Native Ensemble and Folding of a Protein Molten-Globule: Functional Consequence of Downhill Folding

Athi N. Naganathan and Modesto Orozco [Barcelona Supercomputing Center]

J. Am. Chem. Soc., **133**, 12154–12161, 2011.

The continually emerging functional significance of intrinsic disorder and conformational flexibility in proteins has challenged the long-standing dogma of a well-defined structure contributing to a specific function. Here, we dissect the folding mechanism of the α -helical molten-globular protein NCBD from three fundamentally different approaches: statistical-mechanical variable barrier model, C_α -based G $\ddagger$ -model and explicit water all-atom molecular dynamics (MD) simulations.

Protein Dynamics (Cont'd)

Molecular dynamics simulation reveals structural and thermodynamic features of kinase activation by cancer mutations within the epidermal growth factor receptor

Shunzhou Wan and Peter V. Coveney [University College London]

J. Comp. Chem. **32**, 2843–2852, 2011.

The epidermal growth factor receptor (EGFR) is a major target for drugs in treating lung carcinoma as it promotes cell growth and tumor progression. Structural studies have demonstrated that EGFR exists in an equilibrium between catalytically active and inactive forms, and dramatic conformational transitions occur during its activation. It is known that EGFR mutations promote such conformational changes that affect its activation and drug efficacy. In a recent article, we have studied changes in drug binding affinities due to cancer mutations of EGFR using ensemble molecular dynamics (MD) simulations. Here, we address an enhanced activation mechanism thought to be associated with this mutation.

EPR Spectra and Molecular Dynamics Agree That the Nucleotide Pocket of Myosin V Is Closed and That It Opens on Binding Actin

Thomas J. Purcell, Nariman Naber, Shirley Sutton, Roger Cooke, Edward Pate [Washington State University]

J. Molec. Bio. **411**, 16-26, 2011.

We have used EPR spectroscopy and computational modeling of nucleotide-analog spin probes to investigate conformational changes at the nucleotide site of myosin V. We find that, in the absence of actin, the mobility of a spin-labeled diphosphate analog [spin-labeled ADP (SLADP)] bound at the active site is strongly hindered, suggesting a closed nucleotide pocket. The mobility of the analog increases when the MV·SLADP complex (MV = myosin V) binds to actin, implying an opening of the active site in the A·MV·SLADP complex (A = actin).

A Concerted Mechanism for Opening the GDP Binding Pocket and Release of the Nucleotide in Hetero-Trimeric G-Proteins

Maxime Louet, David Perahia, Jean Martinez, Nicolas Floquet [Université Montpellier 1–Université Montpellier 2]

J. Molec. Bio. **411**, 298-312, 2011.

G-protein hetero-trimers play a fundamental role in cell function. Their dynamic behavior at the atomic level remains to be understood. We have studied the Gi hetero-trimer through a combination of molecular dynamics simulations and normal mode analyses. We showed that these big proteins could undergo large-amplitude conformational changes, without any energy penalty and with an intrinsic dynamics centered on their GDP binding pocket. Among the computed collective motions, one of the modes (mode 17) was particularly able to significantly open both the base and the phosphate sides of the GDP binding pocket.

Flexibility of the exportins Cse1p and Xpot depicted by elastic network model

Mingwen Hu and Byung Kim [University of Massachusetts]

J. Mol.Mod., **17**, 1735-1741, 2011.

Nucleocytoplasmic transport in eukaryotic cells involves many interactions between macromolecules, and has been an active area for many researchers. However, the precise mechanism still evades us and more efforts are needed to better understand it. In this study, the authors investigated exportins (Cse1p and Xpot) by elastic network interpolation (ENI) and elastic network based normal mode analysis (EN-NMA). Results of the study on Cse1p were in good agreement with the results obtained by molecular dynamics simulation in another study but with the benefit of time-efficiency.

Protein Dynamics (Cont'd)

Effect of the SH3-SH2 domain linker sequence on the structure of Hck kinase

Heike Meiselbach and Heinrich Sticht [Friedrich-Alexander-Universität]

J. Mol.Mod., **17**, 1927-1934, 2011.

The coordination of activity in biological systems requires the existence of different signal transduction pathways that interact with one another and must be precisely regulated. The Src-family tyrosine kinases, which are found in many signaling pathways, differ in their physiological function despite their high overall structural similarity. We performed comparative molecular dynamics simulations of wildtype Hck and of a mutant Hck in which the SH3-SH2 domain linker is replaced by the corresponding sequence from the homologous kinase Lck.

Structural studies of biologically active glycosylated polyamidoamine (PAMAM) dendrimers

Teresa Silva Barata, Sunil Shaunak, Ian Teo, Mire Zloh [University of London] and Steve Brocchini

J. Mol.Mod., **17**, 2051-2060, 2011.

The partial modification of carboxylic acid terminated polyamidoamine (PAMAM) dendrimers with glucosamine has been reported to give dendrimer glucosamine conjugates novel immuno-modulatory and anti-angiogenic properties. Experimental analysis of these glycosylated dendrimers showed that, on average, eight glucosamine molecules were covalently bound to each dendrimer. In order to better understand the surface loading and distribution of these glucosamine molecules, molecular reactivity was determined by evaluation of electronic properties using frontier molecular orbital theory (FMOT) and molecular dynamics simulations.

The Effect of Mutations on the Alloreactive T Cell Receptor/Peptide-MHC Interface Structure: A Molecular Dynamics Study

Mikhail Y. Wolfson, Kwangho Nam, and Arup K. Chakraborty [Massachusetts Institute of Technology]

J. Phys. Chem. B., **115**, 8317-8327, 2011.

T cells orchestrate adaptive, pathogen-specific immune responses. T cells have a surface receptor (called TCR) whose ligands are complexes (pMHCs) of peptides (derived from pathogens or host proteins) and major histocompatibility complex proteins (MHCs). MHC proteins vary between hosts. During organ transplants, host TCRs interact with peptides present in complex with genetically different MHCs. To explore the origin of this puzzle, we used molecular dynamics simulations to study the dependence of the TCR/pMHC interface on changes in both the peptide and the TCR.

Multiprotein Interactions during Surface Adsorption: a Molecular Dynamics Study of Lysozyme Aggregation at a Charged Solid Surface

Karina Kubiak-Ossowska and Paul A. Mulheran [University of Strathclyde]

J. Phys. Chem. B., **115**, 8891-8900, 2011.

Multiprotein adsorption of hen egg white lysozyme at a model charged ionic surface is studied using fully atomistic molecular dynamics simulations. Simulations with two, three, and five proteins, in various orientations with respect the surface, are performed over a 100 ns time scale. Mutated proteins with point mutations at the major (Arg128 and Arg125) and minor (Arg68) surface adsorption sites are also studied. The 100 ns time scale used is sufficient to observe protein translations, rotations, adsorption, and aggregation.

Protein Dynamics (Cont'd)

Modeling the Tetraphenylalanine-PEG Hybrid Amphiphile: From DFT Calculations on the Peptide to Molecular Dynamics Simulations on the Conjugate

David Zanuy, Ian W. Hamley, and Carlos Aleman
[Universitat Politècnica de Catalunya]

J. Phys. Chem. B., **115**, 8937–8946, 2011.

The conformational properties of the hybrid amphiphile formed by the conjugation of a hydrophobic peptide with four phenylalanine (Phe) residues and hydrophilic poly(ethylene glycol), have been investigated using quantum mechanical calculations and atomistic molecular dynamics simulations. The intrinsic conformational preferences of the peptide were examined using the building-up search procedure combined with B3LYP/6-31G(d) geometry optimizations, which led to the identification of 78, 78, and 92 minimum energy structures for the peptides containing one, two, and four Phe residues.

Ions and the Protein Surface Revisited: Extensive Molecular Dynamics Simulations and Analysis of Protein Structures in Alkali-Chloride Solutions

Ran Friedman [Linnæus University]

J. Phys. Chem. B., **115**, 9213–9223, 2011.

Proteins interact with ions in various ways. The surface of proteins has an innate capability to bind ions, and it is also influenced by the screening of the electrostatic potential owing to the presence of salts in the bulk solution. Alkali metal ions and chlorides interact with the protein surface, but such interactions are relatively weak and often transient. In this paper, computer simulations and analysis of protein structures are used to characterize the interactions between ions and the protein surface.

SymmRef: A flexible refinement method for symmetric multimers

Efrat Mashiach-Farkash, Ruth Nussinov and Haim J. Wolfson
[Tel Aviv University]

Proteins: Stru. Fun. and Bioinfo. **79**, 2607–2623, 2011.

Symmetric protein complexes are abundant in the living cell. Predicting their atomic structure can shed light on the mechanism of many important biological processes. Symmetric docking methods aim to predict the structure of these complexes given the unbound structure of a single monomer, or its model. Symmetry constraints reduce the search-space of these methods and make the prediction easier compared to asymmetric protein-protein docking. However, the challenge of modeling the conformational changes that the monomer might undergo is a major obstacle. In this article, we present SymmRef, a novel method for refinement and reranking of symmetric docking solutions.

Structural analysis of the N-terminal fragment of the antiangiogenic protein endostatin: A molecular dynamics study

Pedro Henrique Monteiro Torres [Universidade Federal do Rio de Janeiro], Gabriel Limaverde Soares Costa Sousa and Pedro Geraldo Pascutti

Proteins: Stru. Fun. and Bioinfo. **79**, 2684–2692, 2011.

Endostatin is a potent antiangiogenic protein derived from the noncollagenous domain 1 (NC1) of collagen XVIII. The mechanism by which endostatin exerts its antiangiogenic effect is still incompletely understood. It has been shown that the 27 amino acid N-terminal fragment of murine endostatin has antitumor, antimigration, and antipermeability activities comparable to the full soluble protein. To understand how this peptide can exert such elaborate function, we performed structural analysis using molecular dynamics to evaluate the behavior of this fragment in aqueous environment.

Protein Dynamics (Cont'd)

TSAR, a new graph-theoretical approach to computational modeling of protein side-chain flexibility: Modeling of ionization properties of proteins

Oleg V. Stroganov, Fedor N. Novikov, Alexey A. Zeifman, Viktor S. Stroylov and Ghermes G. Chilov [Russian Federation, Moscow 119992]

Proteins: Stru. Fun. and Bioinfo. **79**, 2693–2710, 2011.

A new graph-theoretical approach called thermodynamic sampling of amino acid residues (TSAR) has been elaborated to explicitly account for the protein side chain flexibility in modeling conformation-dependent protein properties. In TSAR, a protein is viewed as a graph whose nodes correspond to structurally independent groups and whose edges connect the interacting groups. Each node has its set of states describing conformation and ionization of the group, and each edge is assigned an array of pairwise interaction potentials between the adjacent groups.

Free Energy Calculations

Free energy calculations of protein–ligand interactions

Anita de Ruiter, Chris Oostenbrink [BOKU – University of Natural Resources and Life Sciences]

Curr. Opin. Chem. Biol., **15**, 547-552, 2011.

In the calculation of free energies of binding for protein–ligand complexes, we distinguish endpoint methods, methods involving alchemical modifications and methods that physically displace the ligand from the protein. Most methodological advances seem to come from a clever combination of multiple existing methods to enhance the sampling or to utilize specific advantages of various approaches. The coupling parameters common in thermodynamic integration and in Hamiltonian replica exchange are for instance combined to yield replica exchange thermodynamic integration.

A chirality-based metrics for free-energy calculations in biomolecular systems

Adriana Pietropaolo [Università di Catania], Davide Branduardi, Massimiliano Bonomi and Michele Parrinello

J. Comp. Chem. **32**, 2627–2637, 2011.

In this work, we exploit the chirality index introduced in (Pietropaolo et al., *Proteins* 2008, 70, 667) as an effective descriptor of the secondary structure of proteins to explore their complex free-energy landscape. We use the chirality index as an alternative metrics in the path collective variables (PCVs) framework and we show in the prototypical case of the C-terminal domain of immunoglobulin binding protein GB1 that relevant configurations can be efficiently sampled in combination with well-tempered metadynamics.

Using Free Energy of Binding Calculations To Improve the Accuracy of Virtual Screening Predictions

Robert D. Malmstrom and Stanley J. Watowich [University of Texas Medical Branch]

J.Chem. Infor. and Mod. **51**, 1648–1655, 2011.

Virtual screening of small molecule databases against macromolecular targets was used to identify binding ligands and predict their lowest energy bound conformation (i.e., pose). AutoDock4-generated poses were rescored using mean-field pathway decoupling free energy of binding calculations and evaluated if these calculations improved virtual screening discrimination between bound and nonbound ligands. Two small molecule databases were used to evaluate the effectiveness of the rescoring algorithm in correctly identifying binders of L99A T4 lysozyme.

Free Energy Calculations (Cont'd)

Effects of Biomolecular Flexibility on Alchemical Calculations of Absolute Binding Free Energies

Morgan Lawrenz, Riccardo Baron [University of California, San Diego], Yi Wang, and J. Andrew McCammon

J. Chem. Theor. and Comp. **7**, 2224–2232, 2011.

The independent trajectory thermodynamic integration (IT-TI) approach (Lawrenz, M., et al. *J. Chem. Theory. Comput.* 2009, **5**, 1106–1116) for free energy calculations with distributed computing is employed to study two distinct cases of protein–ligand binding: first, the influenza surface protein N1 neuraminidase bound to the inhibitor oseltamivir, and second, the Mycobacterium tuberculosis enzyme RmlC complexed with the molecule CID 77074. For both systems, finite molecular dynamics (MD) sampling and varied molecular flexibility give rise to IT-TI free energy distributions that are remarkably centered on the target experimental values, with a spread directly related to protein, ligand, and solvent dynamics.

Ligand Binding/Docking

Free Energy Calculations on the Two Drug Binding Sites in the M2 Proton Channel

Ruo-Xu Gu, Limin Angela Liu, Dong-Qing Wei [Shanghai Jiao Tong University], Jian-Guo Du, Lei Liu, and Hong Liu

J. Am. Chem. Soc., **133**, 10817–10825, 2011.

Two alternative binding sites of adamantane-type drugs in the influenza A M2 channel have been suggested, one with the drug binding inside the channel pore and the other with four drug molecule S-binding to the C-terminal surface. Recent studies have suggested that the pore binding site is more energetically favorable but the external surface binding site may also exist. But, which drug binding site leads to channel inhibition in vivo and how drug-resistant mutations affect these sites is not fully understood. We applied MD simulations and potential of mean force calculations to examine the structures and the free energies associated with these putative drug binding sites in an M2–lipid bilayer system.

Molecular modeling study of checkpoint kinase 1 inhibitors by multiple docking strategies and prime/MM-GBSA calculation

Juan Du, Huijun Sun, Lili Xi, Jiazhong Li, Ying Yang, Huanxiang Liu and Xiaojun Yao [Lanzhou University]

J. Comp. Chem. **32**, 2800–2809, 2011.

Developing chemicals that inhibit checkpoint kinase 1 (Chk1) is a promising adjuvant therapeutic to improve the efficacy and selectivity of DNA-targeting agents. Reliable prediction of binding-free energy and binding affinity of Chk1 inhibitors can provide a guide for rational drug design. In this study, multiple docking strategies and Prime/Molecular Mechanics Generalized Born Surface Area (Prime/MM-GBSA) calculation were applied to predict the binding mode and free energy for a series of benzoisoquinolinones as Chk1 inhibitors.

Molecular dynamics study of small molecule inhibitors of the Bcl-2 family

Stéphane Acoca, Qizhi Cui, Gordon C. Shore and Enrico O. Purisima [National Research Council of Canada]

Proteins: Stru. Fun. and Bioinfo. **79**, 2624–2636, 2011.

We carried out docking and molecular dynamics simulations on ABT-737 and obatoclax, which are inhibitors of the Bcl-2 family of proteins. We modeled the binding mode of ABT-737 with Bcl-x_L, Bcl-2, and Mcl-1 and examined their dynamical behavior. We found that the binding of the chlorobiphenyl end of ABT-737 was quite stable across all three proteins. However, the phenylpiperazine linker group was dramatically more mobile in Mcl-1 compared to either Bcl-x_L or Bcl-2.

Enzyme Catalysis

Promiscuity in Alkaline Phosphatase Superfamily. Unraveling Evolution through Molecular Simulations

Violeta Lopez-Canut, Maite Roca, Juan Bertran, Vicent Moliner, and Inaki Tunon [Universitat de Valencia]

J. Am. Chem. Soc., **133**, 12050–12062, 2011.

We here present a theoretical study of the alkaline hydrolysis of a phosphodiester (methyl p-nitrophenyl phosphate or MpNPP) in the active site of *Escherichia coli* alkaline phosphatase (AP), a monoesterase that also presents promiscuous activity as a diesterase. The analysis of our simulations, carried out by means of molecular dynamics (MD) simulations with hybrid quantum mechanics/molecular mechanics (QM/MM) potentials, shows that the reaction takes place through a D_NA_N or dissociative mechanism, the same mechanism employed by AP in the hydrolysis of monoesters. The promiscuous activity observed in this superfamily can be then explained on the basis of a conserved reaction mechanism.

Conformational Plasticity and Dynamics in the Generic Protein Folding Catalyst SlyD Unraveled by Single-Molecule FRET

Dana Kahra, Michael Kovermann, Christian Löw, Verena Hirschfeld, Caroline Haupt, Jochen Balbach, Christian Gerhard Hübner [Universität zu Lübeck]

J. Molec. Bio. **411**, 781-790, 2011.

The relation between conformational dynamics and chemistry in enzyme catalysis recently has received increasing attention. While, in the past, the mechanochemical coupling was mainly attributed to molecular motors, nowadays, it seems that this linkage is far more general. Single-molecule fluorescence methods are perfectly suited to directly evidence conformational flexibility and dynamics. By labeling the enzyme SlyD, a member of peptidyl-prolyl cis-trans isomerases of the FK506 binding protein type with an inserted chaperone domain, with donor and acceptor fluorophores for single-molecule fluorescence resonance energy transfer, we directly monitor conformational flexibility and conformational dynamics between the chaperone domain and the FK506 binding protein domain.

Subunit Interface Dynamics in Hexadecameric Rubisco

Michiel van Lun, David van der Spoel, Inger Andersson [Swedish University of Agricultural Sciences]

J. Molec. Bio. **411**, 1083-1098, 2011.

Ribulose-1,5-bisphosphate (RuBP) carboxylase/oxygenase (Rubisco) plays an important role in the global carbon cycle as a hub for biomass. Rubisco catalyzes not only the carboxylation of RuBP with carbon dioxide but also a competing oxygenation reaction of RuBP with a negative impact on photosynthetic yield. Here, we describe seven different types of interfaces of hexadecameric Rubisco. We have analyzed these interfaces with respect to the size of the interface area and the number of polar interactions, including salt bridges and hydrogen bonds in a variety of Rubisco enzymes from different organisms and different kingdoms of life, including the Rubisco-like proteins.

Enzyme Catalysis (Cont'd)

Computational investigation of the histidine ammonia-lyase reaction: a modified loop conformation and the role of the zinc(II) ion

Amalia-Laura Seff, Sarolta Pilbák, Ioan Silaghi-Dumitrescu and László Poppe [Budapest University of Technology and Economics]

J. Mol. Mod., **17**, 1551–1563, 2011.

Possible reaction intermediates of the histidine ammonia-lyase (HAL) reaction were investigated within the tightly closed active site of HAL from *Pseudomonas putida* (PpHAL). The closed structure of PpHAL was derived from the crystal structure of PpHAL inhibited with L-cysteine, in which the 39–80 loop including the catalytically essential Tyr53 was replaced. This modified loop with closed conformation was modeled using the structure of phenylalanine ammonia-lyase from *Anabaena variabilis* (AvPAL) with a tightly closed active site as a template.

A Computational Approach To Design and Evaluate Enzymatic Reaction Pathways: Application to 1-Butanol Production from Pyruvate

Di Wu, Qin Wang, Rajeev S. Assary, Linda J. Broadbelt [Northwestern University], and Goran Krilov

J. Chem. Infor. and Mod. **51**, 1634–1647, 2011.

We present a new computational strategy for the design and evaluation of novel enzymatic pathways for the biosynthesis of fuels and chemicals. The approach combines the use of the Biochemical Network Integrated Computational Explorer (BNICE) framework and a structure-based screening method for rapid generation and evaluation of novel enzymatic reactions and pathways. The strategy is applied to a case study of 1-butanol production from pyruvate, which yielded nine novel biosynthetic pathways.

Molecular Basis of the Thermostability and Thermophilicity of Laminarinases: X-ray Structure of the Hyperthermostable Laminarinase from *Rhodothermus marinus* and Molecular Dynamics Simulations

Lucas Bleicher, Erica T. Prates, Thiago C. F. Gomes, Rodrigo L. Silveira, Alessandro S. Nascimento, Adriana L. Rojas, Alexander Golubev, Leandro Martínez, Munir S. Skaf, and Igor Polikarpov [University of Sao Paulo]

J. Phys. Chem. B., **115**, 7830–7837, 2011.

Glycosyl hydrolases are enzymes capable of breaking the glycosidic linkage of polysaccharides and have considerable industrial and biotechnological applications. Driven by the later applications, it is frequently desirable that glycosyl hydrolases display stability and activity under extreme environment conditions, such as high temperatures and extreme pHs. Here, we present X-ray structure of the hyperthermophilic laminarinase from *Rhodothermus marinus* (RmLamR) determined at 1.95 Å resolution and molecular dynamics simulation studies aimed to comprehend the molecular basis for the thermal stability of this class of enzymes.

Active Site Gating and Substrate Specificity of Butyrylcholinesterase and Acetylcholinesterase: Insights from Molecular Dynamics Simulations

Lei Fang, Yongmei Pan, Jennifer L. Muzyka, and Chang-Guo Zhan [University of Kentucky]

J. Phys. Chem. B., **115**, 8797–8805, 2011.

Butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) are highly homologous proteins with distinct substrate preferences. In this study we compared the active sites of monomers and tetramers of human BChE and human AChE after performing molecular dynamics (MD) simulations in water-solvated systems. By comparing the conformational dynamics of gating residues of AChE and BChE, we found that the gating mechanisms of the main door of AChE and BChE are responsible for their different substrate specificities.

Protein-Protein Interactions

PROCOS: Computational analysis of protein-protein complexes

Florian Fink, Jochen Hochrein, Vincent Wolowski, Rainer Merkl and Wolfram Gronwald [University of Regensburg]

J. Comp. Chem. **32**, 2575–2586, 2011.

One of the main challenges in protein-protein docking is a meaningful evaluation of the many putative solutions. Here we present a program (PROCOS) that calculates a probability-like measure to be native for a given complex. In contrast to scores often used for analyzing complex structures, the calculated probabilities offer the advantage of providing a fixed range of expected values. This will allow, in principle, the comparison of models corresponding to different targets that were solved with the same algorithm.

SDOCK: A global protein-protein docking program using stepwise force-field potentials

Changsheng Zhang and Luhua La [Peking University]

J. Comp. Chem. **32**, 2598–2612, 2011.

Fast Fourier transform (FFT) method limits the forms of scoring functions in global protein-protein docking. On the other hand, force field potentials can effectively describe the energy hyper surface of biological macromolecules. In this study, we developed a new protein-protein docking program, SDOCK, that incorporates van der Waals attractive potential, geometric collision, screened electrostatic potential, and Lazaridis-Karplus desolvation energy into the scoring function in the global searching process. Stepwise potentials were generated from the corresponding continuous forms to treat the structure flexibility.

Molecular Basis of a Million-Fold Affinity Maturation Process in a Protein-Protein Interaction

Daniel A. Bonsor, Sandra Postel, Brian G. Pierce, Ningyan Wang, Penny Zhu, Rebecca A. Buonpane, Zhiping Weng, David M. Kranz, Eric J. Sundberg [Boston Biomedical Research Institute]

J. Molec. Bio. **411**, 321–328, 2011.

Protein engineering is becoming increasingly important for pharmaceutical applications where controlling the specificity and affinity of engineered proteins is required to create targeted protein therapeutics. Affinity increases of several thousand-fold are now routine for a variety of protein engineering approaches, and the structural and energetic bases of affinity maturation have been investigated in a number of such cases. Here, we present the molecular basis of this affinity increase. Using X-ray crystallography, shotgun reversion/replacement scanning mutagenesis, and computational analysis, we describe, in molecular detail, a process by which extrainterfacial regions of a protein complex can be rationally manipulated to significantly improve protein engineering outcomes.

Conformationally Constrained Peptides from CD2 To Modulate Protein-Protein Interactions between CD2 and CD58

Ameya Gokhale, Thomas K. Weldeghiorghis, Veena Taneja, and Seetharama D. Satyanarayanajois [University of Louisiana at Monroe]

J. Med. Chem. **54**, 5307–5319, 2011.

Cell adhesion molecule CD2 and its ligand CD58 provide good examples of protein-protein interactions in cells that participate in the immune response. To modulate the cell adhesion interaction, peptides were designed from the discontinuous epitopes of the β -strand region of CD2 protein. The two strands were linked by a peptide bond. β -Strands in the peptides were nucleated by inserting a β -sheet-inducing (d)-Pro-Pro sequence or a dibenzofuran (DBF) turn mimetic with key amino acid sequences from CD2 protein that binds to CD58.

Membrane Proteins and Lipid Peptide Interactions

Transfer of Arginine into Lipid Bilayers Is Nonadditive

Justin L. MacCallum, W.F. Drew Bennett, D. Peter Tieleman
[University of Calgary]

Biophysical Journal. **100**, 2394-2402, 2011.

Computer simulations suggest that the translocation of arginine through the hydrocarbon core of a lipid membrane proceeds by the formation of a water-filled defect that keeps the arginine molecule hydrated even at the center of the bilayer. We show here that adding additional arginine molecules into one of these water defects causes only a small change in free energy. The barrier for transferring multiple arginines through the membrane is approximately the same as for a single arginine and may even be lower depending on the exact geometry of the system.

Structural Effects and Translocation of Doxorubicin in a DPPC/Chol Bilayer: The Role of Cholesterol

Tyrone J. Yacoub, Allam S. Reddy, Igal Szleifer
[Northwestern University, Evanston]

Biophysical Journal. **100**, 378-385, 2011.

We use molecular dynamics simulations to characterize the influence of cholesterol (Chol) on the interaction between the anticancer drug doxorubicin (DOX) and a dipalmitoyl phosphatidylcholine/Chol lipid bilayer. We calculate the potential of mean force, which gives us an estimate of the free energy barrier for DOX translocation across the membrane. We find free energy barriers of 23.1 ± 3.1 k_BT, 36.8 ± 5.1 k_BT, and 54.5 ± 4.7 k_BT for systems composed of 0%, 15%, and 30% Chol, respectively.

Aggregation of Model Membrane Proteins, Modulated by Hydrophobic Mismatch, Membrane Curvature, and Protein Class

Daniel L. Parton, Jochen W. Klingelhoefer, Mark S.P. Sansom [University of Oxford]

Biophysical Journal. **100**, 691-699, 2011.

Aggregation of transmembrane proteins is important for many biological processes, such as protein sorting and cell signaling, and also for in vitro processes such as two-dimensional crystallization. We have used large-scale simulations to study the lateral organization and dynamics of lipid bilayers containing multiple inserted proteins. Using coarse-grained molecular dynamics simulations, we have studied model membranes comprising ~7000 lipids and 16 identical copies of model cylindrical proteins of either α -helical or β -barrel types.

Ab Initio prediction of protein–ligand binding structures by replica-exchange umbrella sampling simulations

Hironori Kokubo [Takeda Pharmaceutical Co.], Toshimasa Tanaka and Yuko Okamoto

J. Comp. Chem. **32**, 2810–2821, 2011.

We have developed a prediction method for the binding structures of ligands with proteins. Our method consists of three steps. First, replica-exchange umbrella sampling simulations are performed along the distance between a putative binding site of a protein and a ligand as the reaction coordinate. Second, we obtain the potential of mean force (PMF) of the unbiased system using the weighted histogram analysis method and determine the distance that corresponds to the global minimum of PMF. Third, structures that have this global-minimum distance and energy values around the average potential energy are collected and analyzed using the principal component analysis.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Coarse-Grained Model for PEGylated Lipids: Effect of PEGylation on the Size and Shape of Self-Assembled Structures

Hwankyu Lee [Dankook University] and Richard W. Pastor

J. Phys. Chem. B., **115**, 7830–7837, 2011.

Self-assembly of polyethylene glycol (PEG)-grafted lipids at different sizes and concentrations was simulated using the MARTINI coarse-grained (CG) force field. The interactions between CG PEG and CG dipalmitoylglycerophosphocholine (DPPC)-lipids were parametrized by matching densities of 19-mers of PEG and polyethylene oxide (PEO) grafted to the bilayer from all-atom simulations. Mixtures of lipids and PEG-grafted ($M_w = 550, 1250, \text{ and } 2000$) lipids in water self-assembled to liposomes, bicelles, and micelles at different ratios of lipids and PEGylated lipids.

Spontaneous Buckling of Lipid Bilayer and Vesicle Budding Induced by Antimicrobial Peptide Magainin 2: A Coarse-Grained Simulation Study

Hyung-June Woo [United States Army Medical Research and Materiel Command] and Anders Wallqvist

J. Phys. Chem. B., **115**, 8122–8129, 2011.

Molecular mechanisms of the action of antimicrobial peptides on bacterial membranes were studied by large scale coarse-grained simulations of magainin 2–dipalmitoylphosphatidylcholine / palmitoyloleoylphosphatidylglycerol (DPPC/POPG) mixed bilayer systems with spatial extents up to $0.1 \mu\text{m}$ containing up to 1600 peptides. Equilibrium simulations exhibit disordered toroidal pores stabilized by peptides. However, when a layer of peptides is placed near the lipid head groups on one side of the bilayer only, their incorporation leads to a spontaneous buckling of the bilayer.

The Impact of Texas Red on Lipid Bilayer Properties

Michael J. Skaug, Marjorie L. Longo, and Roland Faller [University of California—Davis, Davis]

J. Phys. Chem. B., **115**, 8500–8505, 2011.

We investigated the impact of fluorescent labeling on the properties of a lipid bilayer using atomistic molecular dynamics simulation. The system consisted of 24 Texas Red–1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine (TR–DHPE) in a bilayer of 488 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) lipids. We found binding between TR–DHPE and DPPC caused by electrostatic interactions. On average, TR–DHPE is bound to 1.2 DPPC molecules.

Structural Dynamics of the S4 Voltage-Sensor Helix in Lipid Bilayers Lacking Phosphate Groups

Magnus Andersson, J. Alfredo Freites, Douglas J. Tobias, and Stephen H. White [University of California, Irvine]

J. Phys. Chem. B., **115**, 8732–8738, 2011.

Voltage-dependent K^+ (Kv) channels require lipid phosphates for functioning. The S4 helix, which carries the gating charges in the voltage-sensing domain (VSD), inserts into membranes while being stabilized by a protein–lipid interface in which lipid phosphates play an essential role. To examine the physical basis of the protein–lipid interface in the absence of lipid phosphates, we performed molecular dynamics (MD) simulations of a KvAP S4 variant (S4mut) in bilayers with and without lipid phosphates.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Combined Use of Replica-Exchange Molecular Dynamics and Magic-Angle-Spinning Solid-State NMR Spectral Simulations for Determining the Structure and Orientation of Membrane-Bound Peptide

Keisuke Ikeda, Tomoshi Kameda, Erisa Harada, Hideo Akutsu, and Toshimichi Fujiwara [Osaka University]

J. Phys. Chem. B., **115**, 9327–9336, 2011.

We report an approach to determining membrane peptides and membrane protein complex structures by magic-angle-spinning solid-state NMR and molecular dynamics simulation. First, an ensemble of low energy structures of mastoparan-X, a wasp venom peptide, in lipid bilayers was generated by replica exchange molecular dynamics (REMD) simulation with the implicit membrane/solvent model. Next, peptide structures compatible with experimental $^{13}\text{C}^\alpha$, C^β , and C' chemical shifts were selected from the ensemble.

Molecular Dynamics Simulations Reveal the Protective Role of Cholesterol in β -Amyloid Protein-Induced Membrane Disruptions in Neuronal Membrane Mimics

Liming Qiu, Creighton Buie, Andrew Reay, Mark W. Vaughn, and Kwan Hon Cheng [Texas Tech University]

J. Phys. Chem. B., **115**, 9795–9812, 2011.

Interactions of β -amyloid ($\text{A}\beta$) peptides with neuronal membranes have been associated with the pathogenesis of Alzheimer's disease (AD); however, the molecular details remain unclear. We used atomistic molecular dynamics (MD) simulations to study the interactions of $\text{A}\beta_{40}$ and $\text{A}\beta_{42}$ with model neuronal membranes. The differences between cholesterol-enriched and depleted lipid domains were investigated by the use of model phosphatidylcholine (PC) lipid bilayers with and without 40 mol % cholesterol.

Protein Folding

Protein Unfolding under Force: Crack Propagation in a Network

Adam M.R. de Graff, Gareth Shannon, Daniel W. Farrell, Philip M. Williams, M.F. Thorpe [Arizona State University, Tempe, Arizona]

Biophysical Journal. **100**, 736–744, 2011.

The mechanical unfolding of a set of 12 proteins with diverse topologies is investigated using an all-atom constraint-based model. Proteins are represented as polypeptides cross-linked by hydrogen bonds, salt bridges, and hydrophobic contacts, each modeled as a harmonic inequality constraint capable of supporting a finite load before breaking. Stereochemically acceptable unfolding pathways are generated by minimally overloading the network in an iterative fashion, analogous to crack propagation in solids.

Simulation of Chaperonin Effect on Protein Folding: A Shift from Nucleation–Condensation to Framework Mechanism

Sebastian Kmiecik and Andrzej Kolinski [University of Warsaw]

J. Am. Chem. Soc., **133**, 10283–10289, 2011.

The iterative annealing mechanism (IAM) of chaperonin-assisted protein folding is explored in a framework of a well-established coarse-grained protein modeling tool, which enables the study of protein dynamics in a time-scale well beyond classical all-atom molecular mechanics. The chaperonin mechanism of action is simulated for two paradigm systems of protein folding, B domain of protein A (BdpA) and B1 domain of protein G (GB1), and compared to chaperonin-free simulations presented here for BdpA and recently published for GB1.

Protein Folding (Cont'd)

A Free-Energy Landscape for Coupled Folding and Binding of an Intrinsically Disordered Protein in Explicit Solvent from Detailed All-Atom Computations

Junichi Higo [Osaka University], Yoshifumi Nishimura, and Haruki Nakamura

J. Am. Chem. Soc., **133**, 10448–10458, 2011.

The N-terminal repressor domain of neural restrictive silencer factor (NRSF) is an intrinsically disordered protein (IDP) that binds to the paired amphipathic helix (PAH) domain of mSin3. An NMR expt revealed that the minimal binding unit of NRSF is a 15-residue segment that has a helical structure upon binding to a cleft of mSin3. We prepare a free-energy landscape of this system by enhanced conformational sampling method, all-atom multicanonical MD. The simulation started from a configuration where the NRSF segment was fully disordered and distant from mSin3 in explicit solvent.

Thermodynamics and Kinetics of the Hairpin Ribozyme from Atomistic Folding/Unfolding Simulations

Lucas G. Nivón, Eugene I. Shakhnovich [Harvard University]

J. Molec. Bio. **411**, 1128–1144, 2011.

We report a set of atomistic folding/unfolding simulations for the hairpin ribozyme using a Monte Carlo algorithm. The hairpin ribozyme folds in solution and catalyzes self-cleavage or ligation via a specific two-domain structure. The minimal active ribozyme has been studied extensively, showing stabilization of the active structure by cations and dynamic motion of the active structure. Here, we introduce a simple model of tertiary-structure formation that leads to a phase diagram for the RNA as a function of temperature and tertiary-structure strength.

Exploring the Folding Free Energy Landscape of a β -Hairpin Miniprotein, Chignolin, Using Multiscale Free Energy Landscape Calculation Method

Ryuhei Harada and Akio Kitao [The University of Tokyo]

J. Phys. Chem. B., **115**, 8806–8812, 2011.

The folding process for a β -hairpin miniprotein, chignolin, was investigated by free energy landscape (FEL) calculations using the recently proposed multiscale free energy landscape calculation method (MSFEL). First, coarse-grained MD simulations searched a broad conformational space, then multiple independent, all-atom MD simulations with explicit solvent determined the detailed local FEL using massively distributed computing. The combination of the two models enabled efficient calculation of the free energy landscapes.

Protein-Nucleic acid Interactions

Theoretical Assessment of the Oligolysine Model for Ionic Interactions in Protein–DNA Complexes

Marcia O. Fenley [Florida State University], Cristina Russo, and Gerald S. Manning

J. Phys. Chem. B., **115**, 9864–9872, 2011.

The observed salt dependence of charged ligand binding to polyelectrolytes, such as proteins to DNA or antithrombin to heparin, is often interpreted by means of the “oligolysine model.” We review this model as derived entirely within the framework of the counterion condensation theory of polyelectrolytes with no introduction of outside assumptions. We update its comparison with experimental data on the structurally simple systems for which it was originally intended. We then compute the salt dependence of the binding free energy for a variety of protein–DNA complexes with nonlinear Poisson–Boltzmann (NLPB) simulation methods.

Nucleic Acids

DNA Modeling Reveals an Extended Lac Repressor Conformation in Classic In Vitro Binding Assays

Andrew D. Hirsh, Todd D. Lillian, Troy A. Lionberger, N.C. Perkins [University of Michigan]

Biophysical Journal. **100**, 718-726, 2011.

Protein-mediated DNA looping, such as that induced by the lactose repressor (LacI) of *Escherichia coli*, is a well-known gene regulation mechanism. Although researchers have given considerable attention to DNA looping by LacI, many unanswered questions about this mechanism. Recent single-molecule observations suggest that the two DNA-binding domains of LacI are capable of splaying open about the tetramerization domain into an extended conformation. We hypothesized that if recent experiments were able to reveal the extended conformation, it is possible that such structures occurred in previous studies as well. In this study, we tested our hypothesis by reevaluating two classic in vitro binding assays using a computational rod model of DNA.

Interactions of Cations with RNA Loop-Loop Complexes

Abhishek Singh, Latsavongsakda Sethaphong, Yaroslava G. Yingling [North Carolina State University]

Biophysical Journal. **100**, 727-735, 2011.

RNA loop-loop interactions are essential in many biological processes, including initiation of RNA folding into complex tertiary shapes, promotion of dimerization, and viral replication. In this article, we examine interactions of metal ions with five RNA loop-loop complexes of unique biological significance using explicit-solvent molecular-dynamics simulations. These simulations revealed the presence of solvent-accessible tunnels through the major groove of loop-loop interactions that attract and retain cations.

A novel computational framework for simultaneous integration of multiple types of genomic data to identify microRNA-gene regulatory modules

Shihua Zhang, Qingjiao Li, Juan Liu, and Xianghong Jasmine Zhou [University of Southern California]

Bioinformatics. **27**, 1684-1690, 2011.

It is well known that microRNAs (miRNAs) and genes work cooperatively to form the key part of gene regulatory networks. However, the specific functional roles of most miRNAs and their combinatorial effects in cellular processes are still unclear. Here we propose an effective data integration framework to identify the miRNA-gene regulatory comodules. The miRNA and gene expression profiles are jointly analyzed in a multiple non-negative matrix factorization framework, and additional network data are simultaneously integrated in a regularized manner.

Structure of Human Telomeric DNA in Crowded Solution

Brahim Heddi and Anh Tuan Phan [Nanyang Technological University]

J. Am. Chem. Soc., **133**, 9824-9833, 2011.

G-quadruplex structures formed by DNA at the human telomeres are attractive anticancer targets. Human telomeric sequences can adopt a diverse range of intramolecular G-quadruplex conformations: a parallel-stranded conformation was observed in the crystalline state, while at least four other forms were seen in K^+ solution, raising the question of which conformation is favored in crowded cellular environment. Here, we report the first NMR structure of a human telomeric G-quadruplex in crowded solution.

Nucleic Acids (Cont'd)

Crowding Promotes the Switch from Hairpin to Pseudoknot Conformation in Human Telomerase RNA

Natalia A. Denesyuk and D. Thirumalai [University of Maryland]

J. Am. Chem. Soc., **133**, 11858–11861, 2011.

Formation of a pseudoknot (PK) in the conserved RNA core domain in the ribonucleoprotein human telomerase is required for function. In vitro experiments show that the PK is in equilibrium with an extended hairpin (HP) structure. We use molecular simulations of a coarse-grained model, which reproduces most of the salient features of the experimental melting profiles of PK and HP, to show that crowding enhances the stability of PK relative to HP in the wild type and in a mutant associated with dyskeratosis congenita.

Nucleotide docking: prediction of reactant state complexes for ribonuclease enzymes

Brigitta Elsässer [University of Paderborn] and Gregor Fels

J. Mol. Mod., **17**, 1953–1962, 2011.

Ribonuclease enzymes (RNases) play key roles in the maturation and metabolism of all RNA molecules. Computational simulations of the processes involved can help to elucidate the underlying enzymatic mechanism and is often employed in a synergistic approach together with biochemical experiments. In order to assist our studies on the cleavage of RNA by the two most important ribonuclease enzymes, RNase A and RNase H, we evaluated four docking tools—MOE2009, Glide 5.5, QXP-Flo+0802, and Autodock 4.0—for their ability to simulate complexes between these enzymes and RNA oligomers.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Advances in the Replacement and Enhanced Replacement Method in QSAR and QSPR Theories

Andrew G. Mercader [Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas], Pablo R. Duchowicz, Francisco M. Fernandez, and Eduardo A. Castro

J. Chem. Infor. and Mod. **51**, 1271–1280, 2011.

The selection of an optimal set of molecular descriptors from a much greater pool of such regression variables is a crucial step in the development of QSAR and QSPR models. The aim of this work is to further improve this important selection process. For this reason three different alternatives for the initial steps of our recently developed enhanced replacement method (ERM) and replacement method (RM) are proposed. These approaches had previously proven to yield near optimal results with a much smaller number of linear regressions than the full search.

Quantitative Structure-Activity Relations (Cont'd)

Online chemical modeling environment (OCHEM): web platform for data storage, model development and publishing of chemical information

Igor V. Tetko [eADMET GmbH], Iurii Sushko, Sergii Novotarskyi, Robert Körner, Anil Kumar Pandey and Matthias Rupp, et al.

J. Comp. Aided Mol. Des. **25**, 533-554, 2011.

The Online Chemical Modeling Environment is a web-based platform that aims to automate and simplify the typical steps required for QSAR modeling. The platform consists of two major subsystems: the database of experimental measurements and the modeling framework. A user-contributed database contains a set of tools for easy input, search and modification of thousands of records. The OCHEM database is based on the wiki principle and focuses primarily on the quality and verifiability of the data. The OCHEM is free for web users and it is available online at <http://www.ochem.eu>.

Potentials and Parameters

Statistical mechanics-based method to extract atomic distance-dependent potentials from protein structures

Sheng-You Huang and Xiaoqin Zou [University of Missouri]

Proteins: Stru. Fun. and Bioinfo. **79**, 2648–2661, 2011.

In this study, we have developed a statistical mechanics-based iterative method to extract statistical atomic interaction potentials from known, nonredundant protein structures. Our method circumvents the long-standing reference state problem in deriving traditional knowledge-based scoring functions, by using rapid iterations through a physical, global convergence function. The rapid convergence of this physics-based method, unlike other parameter optimization methods, warrants the feasibility of deriving distance-dependent, all-atom statistical potentials to keep the scoring accuracy.

Molecular Dynamics

Effect of the F610A Mutation on Substrate Extrusion in the AcrB Transporter: Explanation and Rationale by Molecular Dynamics Simulations

Attilio V. Vargiu [CNR-IOM, Unita SLACS], Francesca Collu, Robert Schulz, Klaas M. Pos, Martin Zacharias, Ulrich Kleinekathofer, and Paolo Ruggerone

J. Am. Chem. Soc., **133**, 10704–10707, 2011.

The tripartite efflux pump AcrAB-TolC is responsible for the intrinsic and acquired multidrug resistance in *Escherichia coli*. Its active part, the homotrimeric transporter AcrB, is in charge of the selective binding of substrates and energy transduction. The mutation F610A has been shown to significantly reduce the minimum inhibitory concentration of doxorubicin and many other substrates, although F610 does not appear to interact strongly with them. In this work, we assess the impact of the F610A mutation on the functionality of AcrB by means of computational techniques, using doxorubicin as substrate.

Molecular Dynamics (Cont'd)

A comparison of neighbor search algorithms for large rigid molecules

Svetlana Artemova [INRIA Grenoble - Rhone-Alpes Research Center], Sergei Grudinin and Stephane Redon

J. Comp. Chem. **32**, 2865–2877, 2011.

Fast determination of neighboring atoms is an essential step in molecular dynamics simulations or Monte Carlo computations, and there exists a variety of algorithms to efficiently compute neighbor lists. However, most of these algorithms are general, and not specifically designed for a given type of application. In this article, we study the case of detecting neighbors between large rigid molecules, which has applications in, e.g., rigid body molecular docking, Monte Carlo simulations of molecular self-assembly or diffusion, and rigid body molecular dynamics simulations.

Predictive Power of Molecular Dynamics Receptor Structures in Virtual Screening

Sara E. Nichols, Riccardo Baron [University of California San Diego], Anthony Ivetac, and J. Andrew McCammon

J.Chem. Infor. and Mod. **51**, 1439–1446, 2011.

Molecular dynamics (MD) simulation is a well-established method for understanding protein dynamics. Conformations from unrestrained MD simulations have yet to be assessed for blind virtual screening (VS) by docking. This study presents a critical analysis of the predictive power of MD snapshots to this regard, evaluating two well-characterized systems of varying flexibility in ligand-bound and unbound configurations. Results from such VS predictions are discussed with respect to experimentally determined structures.

Generalized Normal Coordinates for the Vibrational Analysis of Molecular Dynamics Simulations

Gerald Mathias [Ludwig–Maximilians Universitat Munchen] and Marcel D. Baer

J. Chem. Theor. and Comp. **7**, 2028–2039, 2011.

The computation of vibrational spectra via molecular dynamics (MD) simulations has made lively progress in recent years. In particular, infrared spectra are accessible employing ab initio MD, for which only the total dipole moment has to be computed “on the fly” from the electronic structure along the trajectory. The analysis of such spectra in terms of the normal modes of intramolecular motion, however, still poses a challenge to theory. Here, we present an algorithm to extract such normal modes from MD trajectories by combining several ideas available in the literature.

Block Covariance Overlap Method and Convergence in Molecular Dynamics Simulation

Tod D. Romo and Alan Grossfield [University of Rochester Medical Center]

J. Chem. Theor. and Comp. **7**, 2464–2472, 2011.

Molecular dynamics (MD) is a powerful tool for understanding the fluctuations of biomolecular systems. It is, however, subject to statistical errors in its sampling of the underlying distribution of states. One must understand these errors in order to draw meaningful conclusions from the simulation. This is becoming ever more critical as MD simulations of even larger systems are attempted. We present here a new method for determining the extent of convergence that relies on measures of the fluctuation space sampled by the simulation without any a priori knowledge of states or partitioning of the configuration space.

Molecular Dynamics (Cont'd)

Proton Transfer between Tryptophan and Ionic Liquid Solvents Studied with Molecular Dynamics Simulations

Marco Klahn [Institute of High Performance Computing, 1 Fusionopolis Way], Abirami Seduraman, and Ping Wu

J. Phys. Chem. B., **115**, 8231–8241, 2011.

The reaction free energies and associated pK_a values for proton transfer from positively charged tryptophan ($HTrp^+$) to the two pure ionic liquids (ILs) BMIM- PF_6 and BMIM- BF_4 are derived from molecular simulations. IL solvation effects are examined with molecular dynamics simulations together with an empirical force field in which the average charge distribution in the actual IL is taken into account. A combination of molecular mechanical and quantum mechanical description (QM/MM) is used to examine the protonation of the anion constituents of the ILs.

QM and QM/MM

The Fragmentation–Recombination Mechanism of the Enzyme Glutamate Mutase Studied by QM/MM Simulations

Judith B. Rommel and Johannes Kastner [University of Stuttgart]

J. Am. Chem. Soc., **133**, 10195–10203, 2011.

The radical mechanism of the conversion of glutamate to methylaspartate catalyzed by glutamate mutase is studied with quantum mechanical/molecular mechanical (QM/MM) simulations based on density functional theory (DFT/MM). The hydrogen transfer between the substrate and the cofactor is found to be rate limiting with a barrier of 101.1 kJ mol⁻¹. A careful comparison to the uncatalyzed reaction in water is performed. The protein influences the reaction predominantly electrostatically and to a lesser degree sterically. Our calculations shed light on the atomistic details of the reaction mechanism.

Accurate assessment of the strain energy in a protein-bound drug using QM/MM X-ray refinement and converged quantum chemistry

Zheng Fu, Xue Li and Kenneth M. Merz Jr. [University of Florida]

J. Comp. Chem. **32**, 2587–2597, 2011.

An ongoing question regarding the energetics of protein-ligand binding has been; what is the strain energy that a ligand pays (if any) when binding to its protein target? The traditional method to estimate strain energy uses force fields to calculate the energy difference between the ligand bound conformation and its nearest local minimum/global minimum on the gas-phase or aqueous phase potential energy surface. This makes the implicit assumption that the underlying force field as well as the reference crystal structure is accurate. Herein, we use ibuprofen as a test case and compare MMFF and ab initio QM methods to identify the local and global minimum conformations.

Hybrid QM/MM Calculations on the First Redox Step of the Catalytic Cycle of Bovine Glutathione Peroxidase GPX1

Juraj Kona [Slovak Academy of Sciences] and Walter M. F. Fabian

J. Chem. Theor. and Comp., **7**, 2610–2616, 2011.

The first reaction step of the redox cycle of bovine erythrocyte glutathione peroxidase from class 1 (GPX1) was investigated using hybrid quantum mechanics/molecular mechanics (QM/MM) calculations using the ONIOM methodology. The reduction of hydrogen peroxide by the active-site selenocysteine in selenolate form assisted by the Arg177 residue was modeled based on a proposal from previous molecular dynamics simulations and pK_a calculations (*J. Chem. TheoryComput.* **2010**, 6, 1670–1681).

QM and QM/MM (Cont'd)

Paradynamics: An Effective and Reliable Model for Ab Initio QM/MM Free-Energy Calculations and Related Tasks

Nikolay V. Plotnikov, Shina C. L. Kamerlin, and Arieh Warshel [University of Southern California]

J. Phys. Chem. B., **115**, 7950–7962, 2011.

Recent years have seen tremendous effort in the development of approaches with which to obtain QM/MM free energies for reactions in the condensed phase. Nevertheless, there remain significant challenges to address, particularly, the high computational cost involved in performing proper configurational sampling and, in particular, in obtaining ab initio QM/MM (QM(ai)/MM) free-energy surfaces. We demonstrate the effectiveness of an updated version of our original idea of using a classical reference potential for QM(ai)/MM calculations [*J. Phys. Chem.* 1995, 99, 17516], which we refer to as paradynamics (PD).

Structures of Neutral and Protonated Water Clusters Confined in Predesigned Hosts: A Quantum Mechanical/Molecular Mechanical Study

Zhen Yang, Shugui Hua, Weijie Hua, and Shuhua Li [Nanjing University]

J. Phys. Chem. B., **115**, 8249–8256, 2011.

Hybrid quantum mechanical/molecular mechanical (QM/MM) calculations have been carried out to investigate the structures of the neutral (H₂O)₂₁ and protonated H⁺(H₂O)₂₁ clusters confined in the crystal hosts. The influence of other cocrystallized species and the local electrostatic environments of the crystal hosts on the structures of water clusters has been analyzed. For the neutral (H₂O)₂₁ cluster in the tetrahedral host, its low-lying structures are found to exist as a dodecahedral cage with one interior water molecule, which is in good accord with the corresponding X-ray data.

Nonadiabatic QM/MM Simulations of Fast Charge Transfer in Escherichia coli DNA Photolyase

Paul Benjamin Woiczikowski, Thomas Steinbrecher, Tomas Kubar, and Marcus Elstner [Karlsruhe Institute of Technology]

J. Phys. Chem. B., **115**, 9846–9863, 2011.

In this report, we study the photoactivation process in Escherichia coli DNA photolyase, involving long-range electron transport along a conserved chain of Trp residues between the protein surface and the flavin adenine dinucleotide (FAD) cofactor. Fully coupled nonadiabatic (Ehrenfest) quantum mechanics/molecular mechanics (QM/MM) simulations allow us to follow the time evolution of charge distributions over the natural time scale of multiple charge transfer events and conduct rigorous statistical analysis.

Comparative or Homology Modeling

Structure of the complex between Mucor pusillus pepsin and the key domain of κ-casein for site-directed mutagenesis: a combined molecular modeling and docking approach

Tiezu Li, Jinghui Wang, Yuqiu Li, Zhennai Yang [Northeast Agricultural Research Center of China], Li Zhang and Li Zheng, et al.

J. Mol.Mod., **17**, 1661-1668, 2011.

In the structural-based mutagenesis of Mucor pusillus pepsin (MPP), understanding how κ-casein interacts with MPP is a great challenge for us to explore. Chymosin-sensitive peptide is the key domain of κ-casein that regulates milk clotting through the specific proteolytic cleavage of its peptide bond (Phe105-Met106) by MPP to produce insoluble para-κ-casein. Here, we built the model of this large peptide using molecular modeling technique. Docking study showed that MPP can accommodate the designed model with a favorable binding energy and the docked complex has proven to locally resemble the inhibitor-chymosin complex.

Comparative or Homology Modeling (Cont'd)

A homology model for *Clostridium difficile* methionyl tRNA synthetase: active site analysis and docking interactions

Ehab Al-Moubarak and Claire Simons [Cardiff University]

J. Mol.Mod., **17**, 1679-1693, 2011.

Treatment of *C. difficile* infection is one of the most difficult biomedical challenges. To develop novel antibacterials, researchers have been targeting bacterial molecular functions that are essential for its growth. The methionyl tRNA synthetase (MetRS) is strictly required for protein biosynthesis and success was reported in developing antibacterials to inhibit this enzyme. The present study was aimed at building and analyzing a homology model for *C. difficile* MetRS in the context of drug design. A homology model of *C. difficile* MetRS was constructed using Molecular Operating Environment (MOE) software.

Homology modeling, docking and structure-based pharmacophore of inhibitors of DNA methyltransferase

Jakyung Yoo and José L. Medina-Franco [Torrey Pines Institute for Molecular Studies]

J. Comp. Aided Mol. Des. **25**, 555-567, 2011.

DNA methyltransferase 1 (DNMT1) is an emerging epigenetic target for the treatment of cancer and other diseases. To date, several inhibitors from different structural classes have been published. In this work, we report a comprehensive molecular modeling study of 14 established DNMT1 inhibitors with a herein developed homology model of the catalytic domain of human DNMT1. The geometry of the homology model was in agreement with the proposed mechanism of DNA methylation. Docking results revealed that all inhibitors studied in this work have hydrogen bond interactions with a glutamic acid and arginine residues that play a central role in the mechanism of cytosine DNA methylation.

Internal organization of large protein families: Relationship between the sequence, structure, and function-based clustering

Xiao-Hui Cai, Lukasz Jaroszewski, John Wooley and Adam Godzik [Sanford-Burnham Medical Research Institute]

Proteins: Stru. Fun. and Bioinfo. **79**, 2389–2402, 2011.

The protein universe can be organized in families that group proteins sharing common ancestry. Such families display variable levels of structural and functional divergence, from homogenous families, where all members have the same function and very similar structure, to very divergent families, where large variations in function and structure are observed. For practical purposes of structure and function prediction, it would be beneficial to identify sub-groups of proteins with highly similar structures (iso-structural) and/or functions (iso-functional) within divergent protein families. We compared three algorithms in their ability to cluster large protein families and discuss whether any of these methods could reliably identify such iso-structural or iso-functional groups.

Ligand Docking

Immune system simulation online

Nicolas Rapin, Ole Lund, and Filippo Castiglione [Istituto per le Applicazioni del Calcolo “M.Picone” of the National Research Council of Italy]

Bioinformatics. **27**, 2013-2014, 2011.

The recognition of antigenic peptides is a major event of an immune response. In current mesoscopic-scale simulators of the immune system, this crucial step has been modeled in a very approximated way. We have equipped an agent-based model of the immune system with immuno-informatics methods to allow the simulation of the cardinal events of the antigenic recognition, going from single peptides to whole proteomes.

Identification of cavities on protein surface using multiple computational approaches for drug binding site prediction

Zengming Zhang, Yu Li, Biaoyang Lin, Michael Schroeder, and Bingding Huang [Zhejiang University]

Bioinformatics. **27**, 2083-2088, 2011.

Protein–ligand binding sites are the active sites on protein surface that perform protein functions. Thus, the identification of those binding sites is often the first step to study protein functions and structure-based drug design. There are many computational algorithms and tools developed in recent decades, such as LIGSITEcs/c, PASS, Q-SiteFinder, SURFNET, and so on. In our previous work, MetaPocket, we have proved that it is possible to combine the results of many methods together to improve the prediction result. Here, we continue our previous work by adding four more methods Fpocket, GHECOM, ConCavity and POCASA to further improve the prediction success rate.

Identification of RNA Pseudoknot-Binding Ligand That Inhibits the –1 Ribosomal Frameshifting of SARS-Coronavirus by Structure-Based Virtual Screening

So-Jung Park, Yang-Gyun Kim, and Hyun-Ju Park [Sungkyunkwan University]

J. Am. Chem. Soc., **133**, 10094–10100, 2011.

Programmed –1 ribosomal frameshifting (–1 RF) is an essential regulating mechanism of translation used by SARS-CoV (severe acute respiratory syndrome coronavirus) to synthesize the key replicative proteins encoded by two overlapping open reading frames. The integrity of RNA pseudoknot stability and structure in the –1 RF site is important for efficient –1 RF. Thus, small molecules interacting with high affinity and selectivity with the RNA pseudoknot in the –1 RF site of SARS-CoV (SARS-pseudoknot) would disrupt –1 RF and be fatal to viral infectivity and production. To discover ligands for the SARS-pseudoknot by virtual screening, we constructed a 3D structural model of the SARS-pseudoknot and conducted a computational screening of the chemical database.

Diverse Fragment Clustering and Water Exclusion Identify Protein Hot Spots

John L. Kulp, III, John L. Kulp, Jr., David L. Pompliano, and Frank Guarnieri [BioLeap, Inc.]

J. Am. Chem. Soc., **133**, 10740–10743, 2011.

Simulated annealing of chemical potential located the highest affinity positions of eight organic probes and water on eight static structures of hen egg white lysozyme (HEWL) in various conformational states. In all HELW conformations, a diverse set of organic probes clustered in the known binding site (hot spot). Fragment clusters at other locations were excluded by tightly-bound waters so that only the hot-spot cluster remained in each case. The location of the hot spot was correctly predicted irrespective of the protein conformation and without accounting for protein flexibility during the simulations.

Ligand Docking (Cont'd)

Homology modeling and molecular dynamics simulations of MUC1-9/H-2Kb complex suggest novel binding interactions

Athanassios Stavrakoudis [University of Ioannina], Ioannis G. Tsoulos, Katalin Uray, Ferenc Hudecz and Vasso Apostolopoulos

J. Mol.Mod., **17**, 1817-1829, 2011.

Human MUC1 is over-expressed in human adenocarcinomas and has been used as a target for immunotherapy studies. The 9-mer MUC1-9 peptide has been identified as one of the peptides which binds to murine MHC class I H-2Kb. The structure of MUC1-9 in complex with H-2Kb has been modeled and simulated with classical molecular dynamics, based on the x-ray structure of the SEV9 peptide/H-2Kb complex. Two independent trajectories with the solvated complex (10 ns in length) were produced.

Exploration of the binding of proton pump inhibitors to human P450 2C9 based on docking and molecular dynamics simulation

Rongwei Shi, Jinyu Li, Xiaoning Cao, Xiaolei Zhu [Nanjing University of Technology] and Xiaohua Lu

J. Mol.Mod., **17**, 1941-1951, 2011.

Human P450 protein CYP2C9 is one of the major drug-metabolizing isomers, contributing to the oxidation of 16% of the drugs currently in clinical use. To examine the interaction mechanisms between CYP2C9 and proton pump inhibitors (PPIs), we used molecular docking and MD simulation. Results from molecular docking and MD simulations demonstrate that nine PPIs adopt two different conformations (extended and U-bend structures) at the binding sites and position themselves far above the heme of 2C9.

Interactions of Halichondrin B and Eribulin with Tubulin

Ruoli Bai, Tam Luong Nguyen, James C. Burnett, Onur Atasoylu, Murray H. G. Munro, George R. Pettit, Amos B. Smith, III, Rick Gussio, and Ernest Hamel [National Institutes of Health, Frederick]

J.Chem. Infor. and Mod. **51**, 1393–1404, 2011.

Compounds that modulate microtubule dynamics include highly effective anticancer drugs, leading to continuing efforts to identify new agents and improve the activity of established ones. Here, we demonstrate that [3H]-labeled halichondrin B (HB), a complex, sponge-derived natural product, is bound to and dissociated from tubulin rapidly at one binding site per $\alpha\beta$ -heterodimer, with an apparent K_d of 0.31 μ M. Using MD simulations, we determined complementary conformations of HB and β -tubulin that delineated in atomic detail binding interactions of HB with only β -tubulin, with no involvement of the α -subunit in the binding interaction.

Trifluoperazine regulation of calmodulin binding to Fas: A computational study

Di Pan, Qi Yan, Yabing Chen, Jay M. McDonald and Yuhua Song [The University of Alabama at Birmingham]

Proteins: Stru. Fun. and Bioinfo. **79**, 2543–2556, 2011.

Death-inducing signaling complex (DISC) formation is a critical step in Fas-mediated signaling for apoptosis. Previous experiments have demonstrated that the calmodulin (CaM) antagonist, trifluoperazine (TFP) regulates CaM-Fas binding and affects Fas-mediated DISC formation. In this study, we investigated the anti-cooperative characteristics of TFP binding to CaM and the effect of TFP on the CaM-Fas interaction from both structural and thermodynamic perspectives using combined molecular dynamics simulations and binding free energy analyses.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 32(12), September 2011.

- 2515–2525 **Three-residue loop closure in proteins: A new kinematic method reveals a locus of connected loop conformations**, Ali Nekouzadeh [Washington University in St. Louis] and Yoram Rudy

The closure of a three-residue loop was studied using a developed kinematic method. It was shown that there are infinite number of three-residue loops (a locus of conformations), which can connect two segments of a polypeptide. This adds to the current understanding of a finite number of conformations for three-residue loop-closure.

- 2526–2538 **Quantitative symmetry and chirality—A fast computational algorithm for large structures: Proteins, macromolecules, nanotubes, and unit cells**, Chaim Dryzun, Amir Zait and David Avnir [The Hebrew University of Jerusalem]

See Applications / Protein Structure Analysis.

- 2539–2544 **A novel graphical representation of protein sequences and its application**, Bo Liao, Benyou Liao [Hunan University], Xinguo Lu and Zhi Cao

On the basis of information on the evolution of the 20 amino acids and their physiochemical characteristics, we propose a new two-dimensional (2D) graphical representation of protein sequences in this article.

- 2545–2554 **Alkaline hydrolysis of ethylene phosphate: An ab initio study by supermolecule model and polarizable continuum approach**, Futing Xia and Hua Zhu [Sichuan University]

The alkaline hydrolysis reaction of ethylene phosphate (EP) has been investigated using a supermolecule model, in which several explicit water molecules are included.

- 2555–2563 **Theoretical study on the ring-opening isomerization reaction mechanism of the ring isomers of N_8H_8** , Han-Ying Wu, Wan-Fei Cai, Lai-Cai Li [Sichuan Normal University], An-Min Tian

Ring-opening isomerization from ring-shaped isomers to chain-shaped isomers of N_8H_8 has been studied by a density function B3LYP method at 6-311++G** level.

- 2564–2574 **Molecular mechanical study of halogen bonding in drug discovery**, Mahmoud A. A. Ibrahim [Minia University]

A halogen bond is a noncovalent bond between a halogen atom (X) and a Lewis base (Y). This type of bond is attributed to the anisotropic distribution of the charge density on the halogen atom, resulting in the formation of a positive cap (called the σ -hole) centered on the A–X axis. The current research is the first reported molecular mechanical study of halogen bonding, the positive region centered on the halogen atom was represented by an extra-point (EP) of charge.

- 2575–2586 **PROCOS: Computational analysis of protein–protein complexes**, Florian Fink, Jochen Hochrein, Vincent Wolowski, Rainer Merkl and Wolfram Gronwald [University of Regensburg]

See Applications / Protein Protein Interactions.

- 2587–2597 **Accurate assessment of the strain energy in a protein-bound drug using QM/MM X-ray refinement and converged quantum chemistry**, Zheng Fu, Xue Li and Kenneth M. Merz Jr. [University of Florida]

See Methodology / QM and QM/MM.

- 2598–2612 **SDOCK: A global protein-protein docking program using stepwise force-field potentials**, Changsheng Zhang and Luhua La [Peking University]

See Applications / Protein Protein Interactions.

- 2613–2618 **Water order profiles on phospholipid/cholesterol membrane bilayer surfaces**, David Robinson, Nicholas A. Besley, Paul O'shea and Jonathan D. Hirst [University of Nottingham]

See Applications / Water and Solvation.

- 2619–2626 **Single electron densities: A new tool to analyze molecular wavefunctions**, Arne Lüchow [RWTH Aachen University] and René Petz

A new partitioning scheme for the electron density of a many-electron wavefunction into single electron densities is proposed. These densities are based on the most probable arrangement of the electrons in an atom or molecule.

- 2627–2637 **A chirality-based metrics for free-energy calculations in biomolecular systems**, Adriana Pietropaolo [Università di Catania], Davide Branduardi, Massimiliano Bonomi and Michele Parrinello

See Applications / Free Energy Calculations.

- 2638–2646 **Indexing molecules with chemical graph identifiers**, Elisabet Gregori-Puigjané, Rut Garriga-Sust and Jordi Mestres [Universitat Pompeu Fabra]

Fast and robust algorithms for indexing molecules have been historically considered strategic tools for the management and storage of large chemical libraries. This work introduces a modified and further extended version of the molecular equivalence number naming adaptation of the Morgan algorithm (J Chem Inf Comput Sci 2001, 41, 181-185) for the generation of a chemical graph identifier (CGI).

- 2647–2653 **Derivatives of molecular surface area and volume: Simple and exact analytical formulas**, Konstantin V. Klenin, Frank Tristram, Timo Strunk and Wolfgang Wenzel [Karlsruhe Institute of Technology]

The computational effort of biomolecular simulations can be significantly reduced by means of implicit solvent models in which the energy generally contains a correction depending on the surface area and/or the volume of the molecule.

- 2654–2663 **Theoretical modulation of the color of light emitted by firefly oxyluciferin**, Luís Pinto Da Silva [Universidade do Porto] and Joaquim C. G. Esteves Da Silva

One of the major mysteries regarding firefly bioluminescence is its pH-dependent multicolor variation. At basic pH, the emission is on the yellow–green region, whereas at acid pH, the light emission is observed on the red region of the visible spectrum. Theoretical calculations using density functional theory, molecular mechanics, and semiempirical methods were made to investigate the effect exerted by intermolecular forces on light emission, and their modulation by polarity, and the differences in the conformation of the active site at basic and acid pH.

- 2664–2678 **Combining a polarizable force-field and a coarse-grained polarizable solvent model. II. Accounting for hydrophobic effects**, Michel Masella [Institut de biologie et de technologies de Saclay], Daniel Borgis and Philippe Cuniassé

A revised and improved version of our efficient polarizable force-field/coarse grained solvent combined approach (Masella, Borgis, and Cuniassé, *J. Comput. Chem.* 2008, 29, 1707) is described.

- 2679–2689 **Nonideality in diffusion of ionic and neutral solutes and hydrogen bond dynamics in dimethyl sulfoxide–chloroform mixtures of varying composition**, Rini Gupta and Amalendu Chandra [Indian Institute of Technology, Kanpur]

Molecular dynamics simulations of charged and neutral solutes in dimethyl sulfoxide (DMSO)–chloroform mixtures reveal pronounced nonideality in the solute diffusion with changes of composition of the mixtures.

- 2690–2696 **Gradients for configuration interaction energies with spin-orbit coupling in a semiempirical framework**, Giovanni Granucci [Dipartimento di Chimica e Chimica Industriale] and Maurizio Persico

We present a method for the analytical evaluation of the molecular energy gradient for a semiempirical configuration interaction (CI) wavefunction, taking into account the spin-orbit coupling.

- 2697–2707 **Stepwise disproportionation in polyelectrolyte complexes**, R. S. Dias [Coimbra University], P. Linse and A. A. C. C. Pais

Structural properties and the topology of polyelectrolyte complexes (PECs) formed in solution have been investigated under different conditions by Monte Carlo simulations using a coarse-grained model.

- 2708–2715 **Theoretical study on the unimolecular decomposition of thiophenol**, Ala'a H. Al-Muhtaseb, Mohammednoor Altarawneh [Al-Hussein Bin Talal University], Mansour H. Almatarneh, Raymond A. Poirier and Niveen W. Assaf

The potential energy surface for the unimolecular decomposition of thiophenol (C_6H_5SH) is mapped out at two theoretical levels; BB1K/GTlarge and QCISD(T)/6-311+G(2d,p)//MP2/6-31G(d,p).

- 2716–2726 **A computational study of unique properties of pillar[n]quinones: Self-assembly to tubular structures and potential applications as electron acceptors and anion recognizers**, Ka-un Lao and Ching-hui Yu [National Tsing Hua University]

Density functional theory has been used to calculate the thermodynamic properties and molecular orbitals of pillar[n]quinones.

- 2727–2733 **CORAL: Quantitative structure–activity relationship models for estimating toxicity of organic compounds in rats**, A. P. Toropova, A. A. Toropov [Istituto di Ricerche Farmacologiche Mario Negri], E. Benfenati, G. Gini, D. Leszczynska and J. Leszczynski

For six random splits, one-variable models of rat toxicity (minus decimal logarithm of the 50% lethal dose [pLD50], oral exposure) have been calculated with CORAL software (<http://www.insilico.eu/coral/>).

Journal of Computational Chemistry, 32(13), October 2011.

- 2745–2755 **Reaction rate of propene pyrolysis**, Peipei Han, Kehe Su [Northwestern Polytechnical University], Yan Liu, Yanli Wang, Xin Wang, Qingfeng Zeng, Laifei Cheng and Litong Zhang

The reaction rate of propene pyrolysis was investigated based on the elementary reactions proposed in Qu et al., J Comput Chem 2009, 31, 1421.

- 2756–2764 **Two-level hierarchical parallelization of second-order Møller–Plesset perturbation calculations in divide-and-conquer method**, Michio Katouda, Masato Kobayashi, Hiromi Nakai and Shigeru Nagase [Institute for Molecular Science, Okazaki]

A two-level hierarchical parallelization scheme including the second-order Møller–Plesset perturbation (MP2) theory in the divide-and-conquer method is presented.

- 2765–2773 **Rapid evaluation of the binding energies between peptide amide and DNA base**, Yang Li and Chang-Sheng Wang [Liaoning Normal University]

The binding energies and the equilibrium hydrogen bond distances as well as the potential energy curves of 20 hydrogen-bonded amide–base dimers are evaluated from the analytic potential energy function established in our laboratory recently.

- 2774–2782 **Importance of CH/ π hydrogen bonds in recognition of the core motif in proline-recognition domains: An Ab initio fragment molecular orbital study**, Tomonaga Ozawa [Kissei Pharmaceutical Company Ltd], Kosuke Okazaki and Kazuo Kitaura

We examined CH/ π hydrogen bonds in protein/ligand complexes involving at least one proline residue using the ab initio fragment molecular orbital (FMO) method and the program CHPI.

- 2783–2799 **Discrepancy in the near-solute electric dipole moment calculated from the electric field**, Pei-Kun Yang [I-SHOU University]

The electric dipole moment $\mathbf{p}(\mathbf{r})$ was computed as the integral of the permanent dipole moment of the solvent molecule $\mu(\mathbf{r})$ weighted by the orientational probability distribution $\Omega(\mathbf{r};\mathbf{O})$ over all orientations, where $\mathbf{O}$ is the orientation of the solvent molecule at $\mathbf{r}$.

- 2800–2809 **Molecular modeling study of checkpoint kinase 1 inhibitors by multiple docking strategies and prime/MM–GBSA calculation**, Juan Du, Huijun Sun, Lili Xi, Jiazhong Li, Ying Yang, Huanxiang Liu and Xiaojun Yao [Lanzhou University]

See Applications / Ligand Binding.

- 2810–2821 **Ab Initio prediction of protein–ligand binding structures by replica-exchange umbrella sampling simulations**, Hironori Kokubo [Takeda Pharmaceutical Co.], Toshimasa Tanaka and Yuko Okamoto

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 2822–2835 **Is the spin-orbit coupling important in the prediction of the ^{51}V hyperfine coupling constants of $\text{V}^{\text{IV}}\text{O}^{2+}$ species? ORCA versus Gaussian performance and biological applications**, Giovanni Micera and Eugenio Garribba [Università di Sassari]

Density functional theory calculations of the ^{51}V hyperfine coupling (HFC) tensor **A**, have been completed for eighteen $\text{V}^{\text{IV}}\text{O}^{2+}$ complexes with different donor set, electric charge and coordination geometry.

- 2836–2842 **Optimal scaling factors for CM1 and CM3 atomic charges in RM1-based aqueous simulations**, Jonah Z. Vilseck, Somiseti V. Sambasivarao and Orlando Acevedo [Auburn University]

Scaling factors for atomic charges derived from the RM1 semiempirical quantum mechanical wavefunction in conjunction with CM1 and CM3 charge models have been optimized by minimizing errors in absolute free energies of hydration, ΔG_{hyd} , for a set of 40 molecules.

- 2843–2852 **Molecular dynamics simulation reveals structural and thermodynamic features of kinase activation by cancer mutations within the epidermal growth factor receptor**, Shunzhou Wan and Peter V. Coveney [University College London]

See Applications / Protein Dynamics

- 2853–2864 **Computational protocols for prediction of solute NMR relative chemical shifts. A case study of L-tryptophan in aqueous solution**, Janus J. Eriksen, Jógvan Magnus H. Olsen, K□stutis Aidās, Hans Ågren, Kurt V. Mikkelsen and Jacob Kongsted [University of Southern Denmark]

In this study, we have applied two different spanning protocols for obtaining the molecular conformations of L-tryptophan in aqueous solution, namely a molecular dynamics simulation and a molecular mechanics conformational search with subsequent geometry re-optimization of the stable conformers using a quantum mechanically based method.

- 2865–2877 **A comparison of neighbor search algorithms for large rigid molecules**, Svetlana Artemova [INRIA Grenoble - Rhone-Alpes Research Center], Sergei Grudinin and Stephane Redon

See Methodology / Molecular Dynamics.

- 2878–2889 **Toward a computational tool predicting the stereochemical outcome of asymmetric reactions: Development of the molecular mechanics-based program ACE and application to asymmetric epoxidation reactions**, Nathanael Weill, Christopher R. Corbeil, Joris W. De Schutter and Nicolas Moitessier [McGill University]

The development and application of ACE, a program that predicts the stereochemical outcome of asymmetric reactions is presented.

- 2890–2895 **The effect of polarization on multiple hydrogen-bond formation in models of self-assembling materials**, Yung-Fou Chen and J. J. Dannenberg [City University of New York]

We report density functional theory calculations at the B3LYP/D95(d,p) level on several different cyclic H-bonding dimers, where the monomers of each are connected by a pair of N—H $\cdots$ O=C H-bonding interactions, and the H-bonding donors and acceptors on each monomer are separated by polarizable spacers.

- 2896–2901 **Counterpoise correction is not useful for short and Van der Waals distances but may be useful at long range**, Xiao Wei Sheng, Lukasz Mentel, Oleg V. Gritsenko and Evert Jan Baerends [VU University]

This article investigates the errors in supermolecule calculations for the helium dimer. In a full CI calculation, there are two errors. One is the basis set superposition error (BSSE), the other is the basis set convergence error (BSCE).

- 2902–2908 **Ab initio molecular dynamics of protonated water clusters by integrated multicenter molecular-orbital method**, Taro Udagawa and Shogo Sakai [Gifu University]

To analyze large-scale cluster systems theoretically, we recently developed an “integrated multicenter molecular-orbital” (IMiC-MO) method. This method calculates the force of an entire system by dividing the system into small regions. We used the method to analyze the effect of cluster size and the process of hydrogen bond network (HBN) growth to form H⁺(H₂O)_n (n = 9, 17, and 33) clusters.

- 2909–2923 **Surveying implicit solvent models for estimating small molecule absolute hydration free energies**, Jennifer L. Knight and Charles L. Brooks III [University of Michigan]

See Applications / General and Model Systems.

Journal of Molecular Modeling, 17(7), July, 2011.

- 1531-1535 **Molecular dynamics simulation of ionic conductors: perspectives and limitations**, Dirk Zahn [Universität Erlangen-Nürnberg]

Concepts of modeling ion conductors by means of molecular dynamics simulations are outlined and exemplified by a small series of applications.

- 1537-1550 **3,4,5-Trisubstituted-1,2,4-4H-triazoles as WT and Y188L mutant HIV-1 non-nucleoside reverse transcriptase inhibitors: docking-based CoMFA and CoMSIA analyses**, Elena Cichero [Università degli Studi di Genova], Laura Buffa and Paola Fossa

See Applications / Medicinal Chemistry and Drug Design.

- 1551-1563 **Computational investigation of the histidine ammonia-lyase reaction: a modified loop conformation and the role of the zinc(II) ion**, Amalia-Laura Seff, Sarolta Pilbák, Ioan Silaghi-Dumitrescu and László Poppe [Budapest University of Technology and Economics]

See Applications / Enzyme Catalysis.

- 1565-1577 **Multiple templates-based homology modeling enhances structure quality of AT1 receptor: validation by molecular dynamics and antagonist docking**, Pandian Sokkar, Shylajanaciyar Mohandass and Murugesan Ramachandran [Madurai Kamaraj University]

See Applications / Homology Modeling.

- 1579-1586 **Coupling between the BLUF and EAL domains in the blue light-regulated phosphodiesterase BlrP1**, Maria Khrenova, Tatiana Domratcheva, Bella Grigorenko and Alexander Nemukhin [M.V. Lomonosov Moscow State University]

The first biochemical and structural characterization of the full-length active photoreceptor BlrP1 from *Klebsiella pneumoniae* was recently reported by Barends et al. [Nature 459:1015–1018, (2009)]. We performed molecular dynamics simulations on the dimeric BlrP1 protein in order to examine the coupling regions that are presumably involved in transmitting light-induced structural changes which occur in the BLUF domain to the EAL domain.

- 1587-1598 **Theoretical and experimental studies of vibrational spectra and thermodynamical analysis of 3'-bromopropiophenone and 4'-bromo-3-chloropropiophenone**, Udhayakala Pandian [Pachaiyappa's college], Seshadri Srinivasan, Rajendiran Thanappan Vinayagam and Gunasekaran Sethu

Quantum chemical calculations of molecular geometries, vibrational wavenumbers and thermodynamical properties of 3'-bromopropiophenone and 4'-bromo-3-chloropropiophenone were carried out using Hartree-Fock (HF) and density functional theory (DFT) using hybrid functional B3LYP with 6-31 G (d,p) as basis set.

- 1599-1606 **QSAR study on angiotensin-converting enzyme inhibitor oligopeptides based on a novel set of sequence information descriptors**, Xiaoyu Wang, Juan Wang, Zhihua Lin [Chongqing University of Technology], Yong Lin, Yuan Ding and Yuanqiang Wang, et al.

See Applications / QSAR.

- 1607-1620 **Anti-tubercular drug designing by structure based screening of combinatorial libraries**, Payel Ghosh and Manish C. Bagchi [Indian Institute of Chemical Biology]

See Applications / QSAR.

- 1621-1624 **Quantum chemical modeling of perovskite: An investigation of piezoelectricity in ferrite of yttrium**, Fábio Augusto M. de Lira, Márcio de Souza Farias, Antonio Florêncio de Figueiredo, José Ciriaco Pinheiro [Universidade Federal do Pará], Fábio dos Santos Gil and Marcos Antonio B. dos Santos, et al.

In a previous article, we used Hartree-Fock (HF) theory to study the piezoelectricity in BaTiO₃. In this paper, we applied the Douglas-Kroll-Hess second order scalar relativistic method to investigate the possible piezoelectric properties in the perovskite YFeO₃ structure, which has not yet been studied experimentally.

- 1625-1633 **The mechanism of methanol decomposition by CuO. A theoretical study based on the reaction force and reaction electronic flux analysis**, Maria Luisa Cerón, Barbara Herrera [Pontificia Universidad Católica de Chile], Paulo Araya, Francisco Gracia and Alejandro Toro-Labbé

A theoretical study of methanol decomposition using a model representing the initial step of the reaction $\text{CH}_3\text{OH} + \text{CuO} \rightarrow \text{CH}_2\text{O} + \text{H}_2\text{O} + \text{Cu}$ is presented.

- 1635-1641 **Molecular dynamics studies of human receptor molecule in hemagglutinin of 1918 and 2009 H1N1 influenza viruses**, Angelina Noviani Lee, Yossa Dwi Hartono, Tiedong Sun, Dawei Zhang [Nanyang Technological University], Min Li Leow and Xue-wei Liu, et al.

See Applications / Homology Modeling.

- 1643-1659 **Understanding the structure-activity relationship of betulinic acid derivatives as anti-HIV-1 agents by using 3D-QSAR and docking**, Ping Lan, Wan-Na Chen, Zhi-Jian Huang, Ping-Hua Sun and Wei-Min Chen [Jinan University]

See Applications / Medicinal Chemistry and Drug Design.

- 1661-1668 **Structure of the complex between Mucor pusillus pepsin and the key domain of κ-casein for site-directed mutagenesis: a combined molecular modeling and docking approach**, Tiezhu Li, Jinghui Wang, Yuqiu Li, Zhennai Yang [Northeast Agricultural Research Center of China], Li Zhang and Li Zheng, et al.

See Methodology / Homology Modeling.

- 1669-1678 **Theoretical study of hydrogen bond interactions of fluvastatin with ι-carrageenan and λ-carrageenan**, Anastasios G. Papadopoulos and Michael P. Sigalas [Aristotle University of Thessaloniki]

The binding of the reductase inhibitor drug fluvastatin, hydroxy-3-methylglutaryl coenzyme A, with the hydrophilic ι- or λ-carrageenan polymers, serving as potential controllers of the drug's release rate, have been studied at the density functional level of theory with the B3LYP exchange correlation functional.

- 1679-1693 **A homology model for Clostridium difficile methionyl tRNA synthetase: active site analysis and docking interactions**, Ehab Al-Moubarak and Claire Simons [Cardiff University]

See Methodology / Homology Modeling.

- 1695-1705 **Infrared and electronic absorption spectra of n-butyronitrile and its ions using Møller Plesset method**, Mahadevappa Naganathappa and Ajay Chaudhari [Swami Ramanand Teerth Marathwada University]

We report theoretical infrared and electronic absorption spectra of gauche and anti conformers of n-butyronitrile, their ions and 2-methylpropanenitrile isomer of n-butyronitrile.

- 1707-1717 **The application of inverse Broyden's algorithm for modeling of crack growth in iron crystals,**
Igor Telichev [University of Manitoba] and Oleg Vinogradov

In the present paper we demonstrate the use of inverse Broyden's algorithm (IBA) in the simulation of fracture in single iron crystals.

- 1719-1725 **Theoretical study of structural patterns in CH₂OP₂ isomers,** Raluca Septelean, Petronela Maria Petrar, Nemes Gabriela, Jean Escudié and Ioan Silaghi-Dumitrescu [Babes-Bolyai University]

DFT calculations have been performed on the derivatives of formula CH₂OP₂ to determine their total energy, the relative energy between the isomers and their geometry.

- 1727-1734 **Docking and molecular dynamics study on the inhibitory activity of N, N-disubstituted-trifluoro-3-amino-2-propanols-based inhibitors of cholesteryl ester transfer protein,** Bo-Liang Dong, Qing-Hua Liao and Jing Wei [Tianjin University]

See Applications / Medicinal Chemistry and Drug Design.

- 1735-1741 **Flexibility of the exportins Cse1p and Xpot depicted by elastic network model,** Mingwen Hu and Byung Kim [University of Massachusetts]

See Applications / Protein Dynamics.

- 1743-1753 **Theoretical study on modeling and prediction of optical rotation for biodegradable polymers containing α -amino acids using QSAR approaches,** Shadpour Mallakpour [Isfahan University of Technology], Mehdi Hatami and Hassan Golmohammadi

See Applications / QSAR.

- 1755-1766 **A tool for the morphological analysis of mixtures of lipids and water in computer simulations,** Marc Fuhrmans [University of Groningen] and Siewert-Jan Marrink

See Applications / General and Model Systems.

- 1767-1780 **A versatile approach for modeling and simulating the tacticity of polymers,** Massoud J. Miri [Rochester Institute of Technology], Benjamin P. Pritchard and H. N. Cheng

We are introducing a versatile computerized approach to model and simulate polymer tacticities using seven single-stage statistical models.

- 1781-1800 **Supramolecular synthon pattern in solid clioquinol and cloxiquine (APIs of antibacterial, antifungal, antiaging and antituberculosis drugs) studied by ³⁵Cl NQR, ¹H-17O and ¹H-14N NQDR and DFT/QTAIM,** Jolanta Natalia Latosińska [Adam Mickiewicz University], Magdalena Latosińska, Marzena Agnieszka Tomczak, Janez Seliger and Veselko Žagar

The quinolinol derivatives clioquinol (5-chloro-7-iodo-8-quinolinol, Quinoform) and cloxiquine (5-chloro-8-quinolinol) were studied experimentally in the solid state via ³⁵Cl NQR, ¹H-17O and ¹H-14N NQDR spectroscopies, and theoretically by density functional theory (DFT).

- 1801-1816 **Effect of alkyl substitution on H-bond strength of substituted amide-alcohol complexes**, M. Nagaraju and G. Narahari Sastry [Indian Institute of Chemical Technology]

The effect of alkyl substitution (CH₃, C₂H₅, n-C₃H₇, i-C₃H₇, and t-C₄H₉) on the hydrogen bond strengths (H-bond) of substituted amide-alcohol complexes has been systematically explored.

- 1817-1829 **Homology modeling and molecular dynamics simulations of MUC1-9/H-2Kb complex suggest novel binding interactions**, Athanassios Stavrakoudis [University of Ioannina], Ioannis G. Tsoulos, Katalin Uray, Ferenc Hudecz and Vasso Apostolopoulos

See Methodology / Ligand Binding.

Journal of Molecular Modeling, 17(8), August, 2011.

- 1831-1840 **Identification of novel 5-hydroxy-1H-indole-3-carboxylates with anti-HBV activities based on 3D QSAR studies**, Hui-fang Chai [Guiyang College of Traditional Chinese Medicine], Xin-xia Liang, Lin Li, Chun-shen Zhao and Ping Gong, et al.

See Applications / QSAR.

- 1841-1845 **Lignin-derived oak phenolics: a theoretical examination of additional potential health benefits of red wine**, William N. Setzer [University of Alabama in Huntsville]

Lignin-derived phenolic compounds can be extracted from oak barrels during the aging of red wine, and it is hypothesized that these compounds may contribute to the health benefits of red wine by their antioxidant, radical-scavenging, or chemopreventive activities.

- 1847-1854 **A computational study of CYP3A4 mediated drug interaction profiles for anti-HIV drugs**, Jayakanthan Mannu, Pranitha Jenardhanan and Premendu P. Mathur [Pondicherry University]

See Applications / Medicinal Chemistry and Drug Design.

- 1855-1862 **Atomistic simulations of materials for optical chemical sensors: DFT-D calculations of molecular interactions between gas-phase analyte molecules and simple substrate models**, Andrey A. Safonov, Elena A. Rykova, Alexander A. Bagaturyants [Russian Academy of Sciences], Vyacheslav A. Sazhnikov and Michael V. Alfimov

The structures of complexes of some small molecules (formaldehyde, acetaldehyde, ammonia, methylamine, methanol, ethanol, acetone, benzene, acetonitrile, ethyl acetate, chloroform, and tetrahydrofuran, considered as possible analytes) with ethylbenzene and silanol (C₆H₅C₂H₅ and SiH₃OH, considered as models of polystyrene and silica gel substrates) and with acridine (C₁₃H₉N, considered as a model of an indicator dye

molecule of the acridine series) and the corresponding interaction energies have been calculated using the DFT-D approximation.

- 1863-1875 **Prediction of a new class of RNA recognition motif**, Núria Cerdà-Costa, Jaume Bonet, M. Rosario Fernández, Sandra Villegas [Universitat Autònoma de Barcelona], Francesc X. Avilés and Baldomero Oliva, et al.

The observation that activation domains (AD) of procarboxypeptidases are rather long compared to the pro-regions of other zymogens raises the possibility that they could play additional roles apart from precluding enzymatic activity within the proenzyme and helping in its folding process. In the present work, we compared the overall pro-domain tertiary structure with several proteins belonging to the same fold in the structural classification of proteins (SCOP) database by using structure and sequence comparisons.

- 1877-1890 **Computational study of the Na⁺/H⁺ antiporter from *Vibrio parahaemolyticus***, Assaf Ganoth [The Hebrew University of Jerusalem], Raphael Alhadeff and Isaiah T. Arkin

Sodium proton antiporters are ubiquitous membrane proteins that catalyze the exchange of Na⁺ for protons throughout the biological world. In this study, we utilized a combination of computational methodologies in order to construct a structural model for the Na⁺/H⁺ antiporter from the gram-negative bacterium *Vibrio parahaemolyticus*.

- 1891-1897 **Time-dependent density functional theory study of the excited-state dihydrogen bonding: clusters of 2-pyridone with diethylmethylsilane and triethylgermanium**, Ning-Ning Wei, Ce Hao [Dalian University of Technology], Jiao-Jie Tan, Guangyan Zhao and Ruizhou Li, et al.

Density functional theory (DFT) was carried out to identify the existence of intermolecular dihydrogen bonds of the 2-pyridone (2PY)-diethylmethylsilane (DEMS) and 2PY-triethylgermanium (TEGH) clusters in the ground state.

- 1899-1909 **Integrating molecular docking, DFT and CoMFA/CoMSIA approaches for a series of naphthoquinone fused cyclic α -aminophosphonates that act as novel topoisomerase II inhibitors**, Yi Ma, Jian-Guo Wang [Nankai University], Bin Wang and Zheng-Ming Li

See Applications / Medicinal Chemistry and Drug Design.

- 1911-1918 **Probing solvation decay length in order to characterize hydrophobicity-induced bead-bead attractive interactions in polymer chains**, Siddhartha Das and Suman Chakraborty [Indian Institute of Technology]

In this paper, we quantitatively demonstrate that exponentially decaying attractive potentials can effectively mimic strong hydrophobic interactions between monomer units of a polymer chain dissolved in aqueous solvent.

- 1919-1926 **Insights into scFv:drug binding using the molecular dynamics simulation and free energy calculation**, Guodong Hu [University of Texas at San Antonio], Qinggang Zhang and L. Y. Chen

Molecular dynamics simulations and free energy calculation have been performed to study how the single-chain variable fragment (scFv) binds methamphetamine (METH) and amphetamine (AMP).

- 1927-1934 **Effect of the SH3-SH2 domain linker sequence on the structure of Hck kinase**, Heike Meiselbach and Heinrich Sticht [Friedrich-Alexander-Universität]

See Applications / Protein Dynamics.

- 1935-1939 **Theoretical investigations of the $H\cdots\pi$ and X ($X = F, Cl, Br, I$) $\cdots\pi$ complexes between hypohalous acids and benzene**, Qiang Zhao, Dacheng Feng [Shandong University], Youmin Sun, Jingcheng Hao and Zhengting Cai

The $H\cdots\pi$ and X ($X = F, Cl, Br, I$) $\cdots\pi$ interactions between hypohalous acids and benzene are investigated at the MP2/6-311++G(2d,2p) level.

- 1941-1951 **Exploration of the binding of proton pump inhibitors to human P450 2C9 based on docking and molecular dynamics simulation**, Rongwei Shi, Jinyu Li, Xiaoning Cao, Xiaolei Zhu [Nanjing University of Technology] and Xiaohua Lu

See Methodology / Ligand Docking.

- 1953-1962 **Nucleotide docking: prediction of reactant state complexes for ribonuclease enzymes**, Brigitta Elsässer [University of Paderborn] and Gregor Fels

See Applications / Nucleic acids.

- 1963-1972 **Electronic structure study using density functional theory in organic dendrimers**, Rocío-Margarita Gutiérrez-Pérez, Norma Flores-Holguín [Centro de Investigación en Materiales Avanzados], Daniel Glossmann-Mitnik and Luz-Maria Rodríguez-Valdez

The electronic and structural properties of pyrrolic ring derivatives were studied using density functional theory (DFT) in terms of their application as organic semiconductor materials in photovoltaic devices.

- 1973-1984 **Computational synthesis of hydrogenated fullerenes from C60 to C60H60**, Elena F. Sheka [Peoples' Friendship University of Russia]

Hydrogenation from C60 to C60H60 was studied by an unrestricted broken spin symmetry Hartree-Fock approach implemented in semiempirical codes based on the AM1 technique.

- 1985-1996 **Exploring a coarse-grained distributive strategy for finite-difference Poisson-Boltzmann calculations**, Meng-Juei Hsieh and Ray Luo [University of California, Irvine]

We have implemented and evaluated a coarse-grained distributive method for finite-difference Poisson-Boltzmann (FDPB) calculations of large biomolecular systems. This method is based on the electrostatic focusing principle of decomposing a large fine-grid FDPB calculation into multiple independent FDPB calculations, each of which focuses on only a small and a specific portion (block) of the large fine grid.

- 1997-2004 **Theoretical study on the interactions between methanol and imidazolium-based ionic liquids**, Xueying Zhu, Hui Sun, Dongju Zhang [Shandong University] and Chengbu Liu

To better understand the property of the binary systems composing of imidazolium salt, [emim]⁺A⁻ (A=Cl⁻, Br⁻, BF₄⁻, and PF₆⁻) and methanol, we have investigated in detail the interactions of methanol molecule with anions A⁻, cation [emim]⁺, and ion pair [emim]⁺A⁻ of several ionic liquids (ILs) based on 1-ethyl-3-methylimidazolium cation by performing density functional theory calculations.

- 2005-2016 **All-electron scalar relativistic calculation of water molecule adsorption onto small gold clusters,** Xiang-jun Kuang, Xin-qiang Wang [Chongqing University] and Gao-bin Liu

An all-electron scalar relativistic calculation was performed on Au_n H₂O (n=1–13) clusters using density functional theory (DFT) with the generalized gradient approximation at PW91 level.

- 2017-2027 **A new approach for aromaticity criterion based on electrostatic field gradient,** Ali Heydar Pakiari [Shiraz University] and Narges Bagheri

In this research, electric field gradient (EFG), which is the first derivative of electric field, is applied for evaluation of aromaticity of 89 cyclic organic compounds. In our calculations, DFT procedure (b3lyp) with basis set 6-311++G** has been employed, and the obtained electronic structures and frequency test has been done for optimized geometries.

- 2029-2040 **Extrapolation of water and formaldehyde harmonic and anharmonic frequencies to the B3LYP/CBS limit using polarization consistent basis sets,** Aneta Buczek, Teobald Kupka and Małgorzata A. Broda [University of Opole]

The harmonic and anharmonic frequencies of fundamental vibrations in formaldehyde and water were successfully estimated using the B3LYP Kohn-Sham limit. The results obtained with polarization- and correlation-consistent basis sets were fitted with a two-parameter formula.

- 2041-2050 **Molecular modeling study of intercalation complexes of tricyclic carboxamides with d(CCGGCGCCGG)₂ and d(CGCGAATTCGCG)₂,** Athanasia Varvaresou [Technological Educational Institution of Athens] and Kriton Iakovou

Tricyclic dyes with different mesoatoms such as xanthenes (fluorescein, eosin) anthracenes and acridines (proflavine) approved by the Food and Drug Administration (FDA) for use in foods, pharmaceuticals and cosmetic preparations interact with DNA, and some of them do so through intercalation. Hyperchem 7.5, Spartan 04, Yasara 10.5.14 program packages and molecular modeling, molecular mechanics and dynamics techniques with the oligonucleotides d(CCGGCGCCGG)₂ and d(CGCGAATTCGCG)₂ were utilized in order to examine the mode of binding to DNA of a range of tricyclic carboxamides bearing N,N-dimethylaminoethyl side chain.

- 2051-2060 **Structural studies of biologically active glycosylated polyamidoamine (PAMAM) dendrimers,** Teresa Silva Barata, Sunil Shaunak, Ian Teo, Mire Zloh [University of London] and Steve Brocchini

See Applications / Protein Dynamics.

- 2061-2067 **Interactions between alkaline earth cations and oxo ligands. DFT study of the affinity of the Mg²⁺ cation for phosphoryl ligands,** Leonardo Moreira da Costa, José Walkimar de Mesquita Carneiro [Universidade Federal Fluminense] and Lilian Weitzel Coelho Paes

DFT (B3LYP/6-31+G(d)) calculations of Mg²⁺ affinities for a set of phosphoryl ligands were performed.

- 2069-2082 **Cooperative effect of water molecules in the self-catalyzed neutral hydrolysis of isocyanic acid: a comprehensive theoretical study**, Xi-Guang Wei, Xiao-Ming Sun, Xiao-Peng Wu, Song Geng and Yi Ren [Key State Laboratory of Biotherapy, Chengdu], et al.

The detailed reaction mechanism for the water-assisted hydrolysis of isocyanic acid, $\text{HNCO} + \text{H}_2\text{O} \rightarrow \text{CO}_2 + \text{NH}_3$ ($n = 0-6$), taking place in the gas phase, has been investigated. All structures were optimized and characterized at the MP2/6-311++G* level of theory, and then re-optimized at MP2/6-311++G**.

- 2083-2092 **Geometries of stacking interactions between phenanthroline ligands in crystal structures of square-planar metal complexes**, Goran V. Janjić, Predrag V. Petrović, Dragan B. Ninković and Snežana D. Zarić [University of Belgrade]

Stacking interactions of phenanthroline square-planar complexes in crystal structures were studied by analyzing data from the Cambridge Structural Database.

- 2093-2097 **Theoretical study of the electronic properties of fluorographene**, Cristina Nava Contreras, Heriberto Hernandez Cocoltzi and Ernesto Chigo Anota [Benemérita Universidad Autónoma de Puebla]

First-principles calculations were performed for fluorine-decorated graphene (fluorographene). Three different hexagonal clusters were used—circular (C₂₄H₁₂), triangular (C₂₃H₁₀) and rectangular (C₂₄H₁₂)—and the fluorine atoms were randomly distributed in the mesh.

- 2099-2102 **New insight into the formation mechanism of imidazolium-based halide salts**, Xueying Zhu, Dongju Zhang [Shandong University] and Chengbu Liu

By performing density functional theory calculations, the Menshutkin reaction between the N-methyl imidazole with chloroethane is reexamined to rationalize the experimental discovery.

- 2103-2111 **FTIR, Raman, and UV-Vis spectroscopic and DFT investigations of the structure of iron–lead–tellurate glasses**, Simona Rada [Technical University of Cluj-Napoca], Adriana Dehelean and Eugen Culea

In this work, the effects of iron ion intercalations on lead–tellurate glasses were investigated via FTIR, Raman and UV-Vis spectroscopies.

- 2113-2130 **Three-dimensional quantitative structure-activity relationships of pyrrolopyridinone as cell division cycle kinase inhibitors by CoMFA and CoMSIA**, Junxia Zheng, Gaokeng Xiao, Jialiang Guo, Pinghua Sun [Jinan University], Longyi Rao and Wei Chao, et al.

See Applications / QSAR.

4. ADDRESSES OF PRINCIPAL AUTHORS

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1	APPLICATIONS (64)	Page 2		
1.1	Small Molecules (11)			
	Water and Solvation	Page 2	Med. Chem. And Drug	Page 2
1.2	Biopolymers (53)			
	Bioinformatics and Cheminformatics	Page 5	Enzyme Catalysis	Page 13
	Comparative or Homology Modeling	Page 6	Protein-Protein Interactions	Page 14
	Protein Conformational Analysis	Page 7	Membrane Proteins	Page 14
	Protein Dynamics	Page 8	Protein Folding	Page 16
	Free Energy Calculations	Page 11	Nucleic Acids	Page 17
	Ligand Binding	Page 12		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material			
2	METHODOLOGY (28)	Page 19		
	QSAR	Page 19	Monte Carlo	Page 22
	Potentials and Parameters	Page 20	QM & QM/MM	Page 23
	Solvation Energy	Page 21	Comparative or Homology	Page 25
	Molecular Dynamics	Page 21	Ligand Docking	Page 26
3	JOURNAL REVIEWS (2)	Page 27		
	Journal of Computational Chemistry, 32 (15), November, 2011.			
	Journal Of Molecular Modeling, 17(10), October, 2011			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 34		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

On the Role of Water Models in Quantifying the Binding Free Energy of Highly Conserved Water Molecules in Proteins: The Case of Concanavalin A

Elisa Fadda and Robert J. Woods [University of Georgia]

J. Chem. Theor. and Comp., **7**, 3391–3398, 2011.

The ability of ligands to displace conserved water molecules in protein binding sites is of significant interest in drug design and is particularly pertinent in the case of glycomimetic drugs. A synthetic ligand was designed with the aim of displacing such water. While the synthetic ligand bound to Con A in an analogous manner to that of the natural ligand, crystallographic analysis demonstrated that it did not displace the conserved water. In order to quantify the affinity of this particular water for the Con A surface, we report here the calculated standard binding free energy for this water in both ligand-bound and free Con A.

Medicinal Chemistry and Drug Design

Novel human mPGES-1 inhibitors identified through structure-based virtual screening

Adel Hamza, Xinyun Zhao, Min Tong, Hsin-Hsiung Tai, Chang-Guo Zhan [University of Kentucky]

Bioorg. and Med.Chem., **19**, 6077-6086, 2011.

Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible prostaglandin E synthase after exposure to pro-inflammatory stimuli and, therefore, represents a novel target for therapeutic treatment of acute and chronic inflammatory disorders. It is essential to identify mPGES-1 inhibitors with novel scaffolds as new leads or hits for the purpose of drug design and discovery that aim to develop the next-generation anti-inflammatory drugs. Herein we report novel mPGES-1 inhibitors identified through a combination of large-scale structure-based virtual screening, flexible docking, molecular dynamics simulations.



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Medicinal Chemistry and Drug Design (Cont'd)

Multi-target drug discovery in anti-cancer therapy: Fragment-based approach toward the design of potent and versatile anti-prostate cancer agents

Alejandro Speck-Planche, Valeria V. Kleandrova, Feng Luan, M. Natália D.S. Cordeiro [University of Porto]

Bioorg. and Med.Chem., **19**, 6239-6244, 2011.

Prostate cancer (PCa) is the second-leading cause of cancer deaths among men in the around the world. Understanding the biology of PCa is essential to the development of novel therapeutic strategies, in order to prevent this disease. With the pass of the time, PCa cell lines become resistant to the current anti-PCa drugs. For this reason, there is a necessity to develop new anti-PCa agents with the ability to be active against several PCa cell lines. We introduce here the first multi-target approach for the design and prediction of anti-PCa agents against several cell lines.

Synthesis, biological evaluation, and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents

Xiao-Min Zhang, Min Qiu, Juan Sun, Yan-Bin Zhang, Yu-Shun Yang, Xiao-Liang Wang, Jian-Feng Tang, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med.Chem., **19**, 6518-6524, 2011.

A series of new 1,3,4-oxadiazole derivatives containing 1,4-benzodioxan moiety (**6a–6s**) as potential telomerase inhibitors have been designed, synthesized, structurally determined, and their biological activities were also evaluated as potential anticancer agents. The bioassay tests demonstrated that compounds **6k**, **6l**, **6m**, **6n** and **6s** exhibited broad-spectrum antitumor activity with IC₅₀ concentration range from 7.21 μM to 25.87 μM against the four cancer cell lines HEPG2, HELA, SW1116 and BGC823.

Prediction of zanamivir efficiency over the possible 2009 Influenza A (H1N1) mutants by multiple molecular dynamics simulations and free energy calculations

Dabo Pan, Huijun Sun, Chongliang Bai, Huanxiang Liu [Lanzhou University], Yulin Shen and Nengzhi Jin, et al.

J. Mol.Mod., **17**, 2465-2473, 2011.

As one of the most important antiviral drugs against 2009 influenza A (H1N1), will zanamivir be effective for the possible drug resistant mutants? To answer this question, we combined multiple molecular dynamics simulations and molecular mechanics generalized Born surface area (MM-GBSA) calculations to study the efficiency of zanamivir over the most frequent drug-resistant strains of neuraminidase including R293K, R152K, E119A/D and H275Y mutants. The calculated results indicate that the modeled mutants of the 2009-H1N1 strains except H275Y will be significantly resistant to zanamivir.

The role of hydrogen bonds in an aqueous solution of acetylsalicylic acid: a molecular dynamics simulation study

Maria Cristina Donnamaria [CICPBA] and Juan Roberto de Xammar Oro

J. Mol.Mod., **17**, 2485-2490, 2011.

This work focuses on the role of the dynamic hydrogen bonds (HB) formed in an aqueous solution of aspirin using molecular dynamics simulation. The statistics reveal the existence of internal HB that inhibit the rotational movements of the acetyl and the carboxylic acid groups, forcing the molecule to adopt a closed conformer structure in water, and playing an important role in stabilizing this conformation.

Medicinal Chemistry and Drug Design (Cont'd)

Three-Dimensional Pharmacophore Modeling of Liver-X Receptor Agonists

Wenxia Zhao, Qiong Gu, Ling Wang, Hu Ge, Jiabo, Li, and Jun Xu [Sun Yat-Sen University]

J.Chem. Infor. and Mod. **51**, 2147–2155, 2011.

High cholesterol levels contribute to hyperlipidemia. Liver X receptors (LXRs) are the drug targets. LXRs regulate the cholesterol absorption, biosynthesis, transportation, and metabolism. Novel agonists of LXR, especially LXR β , are attractive solutions for treating hyperlipidemia. In order to discover novel LXR β agonists, a three-dimensional pharmacophore model was built based upon known LXR β agonists. The model was validated with a test set, a virtual screening experiment, and the FlexX docking approach. Results show that the model is capable of predicting a LXR β agonist activity.

Conformational Analysis of Aliskiren, a Potent Renin Inhibitor, Using High-Resolution Nuclear Magnetic Resonance and Molecular Dynamics Simulations

Minos-Timotheos Matsoukas, Panagiotis Zoumpoulakis, and Theodore Tselios [University of Patras]

J.Chem. Infor. and Mod. **51**, 2386–2397, 2011.

Aliskiren is a nonpeptide antihypertensive drug that potently inhibits the human enzyme renin in vitro and in vivo. Many clinical trials have shown the efficacy of aliskiren to lower blood pressure in correlation with other antihypertensive agents. In this report, the conformational behavior of aliskiren is studied in water, trifluoroethanol, and dimethylformamide solutions by means of 2D-NMR spectroscopy and molecular dynamics simulations.

Identifying Compound-Target Associations by Combining Bioactivity Profile Similarity Search and Public Databases Mining

Tiejun Cheng, Qingliang Li, Yanli Wang [National Institutes of Health, Maryland], and Stephen H. Bryant

J.Chem. Infor. and Mod. **51**, 2440–2448, 2011.

Molecular target identification is of central importance to drug discovery. Here, we developed a computational approach, named bioactivity profile similarity search (BASS), for associating targets to small molecules by using the known target annotations of related compounds from public databases. To evaluate BASS, a bioactivity profile database was constructed using 4296 compounds that were commonly tested in the US National Cancer Institute 60 human tumor cell line anticancer drug screen (NCI-60).

Inhibitors of Androgen Receptor Activation Function-2 (AF2) Site Identified through Virtual Screening

Peter Axerio-Cilies, Nathan A. Lack, M. Ravi Shashi Nayana, Ka Hong Chan, Anthony Yeung, Eric Leblanc, Emma S. Tomlinson Guns, Paul S. Rennie, and Artem Cherkasov [University of British Columbia]

J.Med.Chem. **54**, 6197–6205, 2011.

The androgen receptor (AR) is one of the most studied drug targets for the treatment of prostate cancer. However, all current anti-androgens directly interact with the AR at the androgen binding site, which is prone to resistant mutations, calling for new strategies of the AR inhibition. The current study represents the first attempt to use virtual screening to identify inhibitors of activation function-2 (AF2) of the human AR. By combining large-scale docking with experimental approaches, we were able to identify several small molecules that interact with the AF2 and effectively prevent the transcriptional activation of the AR.

Medicinal Chemistry and Drug Design (Cont'd)

3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles: A New Scaffold for the Selective Inhibition of Monoamine Oxidase B

Elias Maccioni, Stefano Alcaro [University of Cagliari], Roberto Cirilli, Sara Vigo, Maria Cristina Cardia, Maria Luisa Sanna, Rita Meleddu, Matilde Yanez, Giosue` Costa, Laura Casu, Peter Matyus, and Simona Distinto

J.Med.Chem. **54**, 6394–6398, 2011.

3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles were designed, synthesized, and tested as inhibitors against human monoamine oxidase (MAO) A and B isoforms. Several compounds, obtained as racemates, were identified as selective MAO-B inhibitors. The enantiomers of some derivatives were separated by enantioselective HPLC and tested. The R-enantiomers always showed the highest activity. Docking study and molecular dynamic simulations demonstrated the putative binding mode. We conclude that these 1,3,4-oxadiazoles derivatives are promising reversible and selective MAO-B inhibitors.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SWIFT MODELLER: A JAVA based GUI for molecular modeling

Abhinav Mathur, Shankaracharya and Ambarish S. Vidyarthi [Birla Institute of Technology, Mesra]

J. Mol.Mod., **17**, 2423-2442, 2011.

MODELLER is command line argument based software which requires tedious formatting of inputs and writing of Python scripts which most people are not comfortable with. Also the visualization of output becomes cumbersome due to verbose files. This makes the whole software protocol very complex and requires extensive study of MODELLER manuals and tutorials. Here we describe SWIFT MODELLER, a GUI that automates formatting, scripting and data extraction processes and present it in an interactive way making MODELLER much easier to use than before.

Self-Contained Sequence Representation: Bridging the Gap between Bioinformatics and Cheminformatics

William L. Chen [Accelrys, Incorporated], Burton A. Leland, Joseph L. Durant, David L. Grier, Bradley D. Christie, James G. Nourse, and Keith T. Taylor

J.Chem. Infor. and Mod. **51**, 2186–2208, 2011.

The wide application of next-generation sequencing has presented a new hurdle to bioinformatics for managing the fast-growing sequence data. The management of biomacromolecules at the chemistry level imposes an even greater challenge in cheminformatics because of the lack of a good chemical representation of biopolymers. Here we introduce the self-contained sequence representation (SCSR). SCSR combines the best features of bioinformatics and cheminformatics notations. SCSR is the first general, extensible, and comprehensive representation of biopolymers in a compressed format that retains chemistry detail.

Bioinformatics and Cheminformatics (Cont'd)

SHAFTS: A Hybrid Approach for 3D Molecular Similarity Calculation. 1. Method and Assessment of Virtual Screening

Xiaofeng Liu, Hualiang Jiang, and Honglin Li [East China University of Science and Technology]

J.Chem. Infor. and Mod. **51**, 2372–2385, 2011.

We developed a novel approach called SHAFTS (SHApe-FeaTure Similarity) for 3D molecular similarity calculation and ligand-based virtual screening. SHAFTS adopts a hybrid similarity metric combined with molecular shape and colored (labeled) chemistry groups annotated by pharmacophore features for 3D similarity calculation and ranking, which is designed to integrate the strength of pharmacophore matching and volumetric overlay approaches. SHAFTS is suitable for large-scale virtual screening with single or multiple bioactive compounds as the query “templates” regardless of whether corresponding experimentally determined conformations are available.

Comparative or Homology Modeling

Three Dimensional Models of Cu²⁺-Aβ(1–16) Complexes from Computational Approaches

Jorge Ali´-Torres, Jean-Didier Mare´chal, Luis Rodri´guez-Santiago, and Mariona Sodupe [Universitat Auto´noma de Barcelona]

J. Am. Chem. Soc., **133**, 15008–15014, 2011.

Elucidation of the coordination of metal ions to Aβ is essential to understand their role in its aggregation and to rationally design new chelators with potential therapeutic applications in Alzheimer disease. In this study, we combine homology modeling (HM) techniques with quantum mechanics based approaches (QM) to determine plausible three-dimensional models for Cu²⁺-Aβ(1–16) with three histidines in their coordination sphere.

Computational Design of a Collagen A:B:C-Type Heterotrimer

Fei Xu, Sohail Zahid, Teresita Silva, and Vikas Nanda [Robert Wood Johnson Medical School]

J. Am. Chem. Soc., **133**, 15260–15263, 2011.

We have successfully designed an A:B:C collagen peptide heterotrimer using an automated computational approach. The algorithm maximizes the energy gap between the target and competing misfolded states while enforcing a minimum target stability. Circular dichroism (CD) measurements confirm that all three peptides are required to form a stable, structured triple helix.

Homology model and docking studies on porcine β2 adrenoceptor: description of two binding sites

Marvin A. Soriano-Ursúa [Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón], José Correa-Basurto, José G. Trujillo-Ferrara and Alberto J. Kaumann

J. Mol.Mod., **17**, 2525–2538, 2011.

The affinity of the classical β2 adrenoceptor-selective inverse agonist ICI118,551 is notoriously lower for porcine β2 adrenoceptors (pβ2AR) than for human β2 adrenoceptors (hβ2AR) but molecular mechanisms for this difference are still unclear. Homology 3-D models of pβ2AR can be useful in predicting similarities and differences, which might in turn increase the comparative understanding of ligand interactions with the hβ2AR. In this work, the pβ2AR amino acid sequence was used to carry out homology modeling. The selected pβ2AR 3-D structure was structurally and energetically optimized and used as a model for further theoretical study.

Comparative or Homology Modeling (Cont'd)

In silico study on the substrate binding manner in human myo-inositol monophosphatase 2

Seisuke Fujita, Tetsuo Ohnishi, Shujiro Okuda, Norihisa Fujita [Ritsumeikan University], Ryo Kobayashi and Satoshi Fukuno, et al.

J. Mol. Mod., **17**, 2559-2567, 2011.

The human IMPA2 gene encoding myo-inositol monophosphatase 2 is highly implicated with bipolar disorder but the substrates and the reaction mechanism of myo-inositol monophosphatase 2 have not been well elucidated.⁹ In the present study, we constructed 3D models of three- and two-Mg²⁺-ion bound myo-inositol monophosphatase 2, and studied substrate-binding manners using the docking program AutoDock3.

Selection of In Silico Drug Screening Results for G-Protein-Coupled Receptors by Using Universal Active Probes

Mitsuhiro Wada, Eiji Kanamori, Haruki Nakamura, and Yoshifumi Fukunishi [(AIST), Tokyo]

J. Chem. Infor. and Mod. **51**, 2398–2407, 2011.

We developed a new protocol for in silico drug screening for G-protein-coupled receptors (GPCRs) using a set of “universal active probes” (UAPs) with an ensemble docking procedure. UAPs are drug-like compounds, which are actual active compounds of a variety of known proteins. The current targets were nine human GPCRs whose three-dimensional (3D) structures are unknown, plus three GPCRs, namely β_2 -adrenergic receptor (ADRB2), A_{2A} adenosine receptor (A_{2A}), and dopamine D3 receptor (D₃), whose 3D structures are known.

Charybdotoxin Unbinding from the mKv1.3 Potassium Channel: A Combined Computational and Experimental Study

Morteza Khabiri, Azadeh Nikouee, Lukasz Cwiklik, Stephan Grissmer, and Rüdiger Ettrich [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **115**, 11490–11500, 2011.

Charybdotoxin, belonging to the group of so-called scorpion toxins, is a short peptide able to block many voltage-gated potassium channels, such as mKv1.3, with high affinity. We use a reliable homology model based on the high-resolution crystal structure of the 94% sequence identical homologue Kv1.2 for charybdotoxin docking followed by molecular dynamics simulations to investigate the mechanism and energetics of unbinding, tracing the behavior of the channel protein and charybdotoxin during umbrella-sampling simulations as charybdotoxin is moved away from the binding site.

Protein Conformational Analysis

Optimization of van der Waals Energy for Protein Side-Chain Placement and Design

Amr Fahmy, Gerhard Wagner [Harvard Medical School]

Biophysical Journal. **101**, 1690-1698, 2011.

Computational determination of optimal side-chain conformations in protein structures has been a long-standing and challenging problem. To address this we have developed an algorithm for generating a set of side-chain conformations that is dense enough that at least one of its members would have a root mean-square deviation of no more than R Å from any possible side-chain conformation of the amino acid.

Protein Conformational Analysis (Cont'd)

Local Conformational Flexibility Provides a Basis for Facile Polymer Formation in Human Neuroserpin

Anindya Sarkar, Crystal Zhou, Robert Meklumburg, Patrick L. Wintrobe [Case Western Reserve University]

Biophysical Journal. **101**, 1758-1765, 2011.

Neuroserpin is a regulator of neuronal growth and plasticity. Like other members of the serpin family, neuroserpin undergoes a large conformational change as part of its function. Unlike other serpins such as α_1 -antitrypsin, wild-type neuroserpin will polymerize under near-physiological conditions, and will spontaneously transition to the latent state. To probe the origins of this conformational lability, we have performed hydrogen exchange measurements and molecular-dynamics simulations on human neuroserpin.

Protein Dynamics

On the Minimization of Fluctuations in the Response Times of Autoregulatory Gene Networks

Rajamanickam Murugan, Gabriel Kreiman [Harvard Medical School]

Biophysical Journal. **101**, 1297-1306, 2011.

The temporal dynamics of the concentrations of several proteins are tightly regulated, particularly for critical nodes in biological networks such as transcription factors. An important mechanism to control transcription factor levels is through autoregulatory feedback loops where the protein can bind its own promoter. Here we use theoretical tools and computational simulations to further our understanding of transcription-factor autoregulatory loops.

Relation between Molecular Shape and the Morphology of Self-Assembling Aggregates: A Simulation Study

Robert Vácha [University of Cambridge], Daan Frenkel

Biophysical Journal. **101**, 1432-1439, 2011.

Proteins can aggregate in a wide variety of structures, both compact and extended. We present simulations of a coarse-grained anisotropic model that reproduce many of the experimentally observed aggregate structures. Conversely, all structures predicted by our model have experimental counterparts (ribbons, multistranded fibrils, and vesicles). The model we use is that of a rodlike particle with an attractive (hydrophobic) stripe on its side.

Multiscale Ensemble Modeling of Intrinsically Disordered Proteins: p53 N-Terminal Domain

Tsuyoshi Terakawa, Shoji Takada [Kyoto University]

Biophysical Journal. **101**, 1450-1458, 2011.

Intrinsically disordered proteins (IDPs) are ubiquitous and play key roles in transcriptional regulations and other cellular processes. To characterize diverse structural ensembles of IDPs, combinations of NMR and computational modeling showed some promise, but they need further improvements. Here, for accurate and efficient modeling of IDPs, we propose a systematic multiscale computational method. We first perform all-atom replica-exchange molecular dynamics (MD) simulations of a few fragments selected from a target IDP.

Protein Dynamics (Cont'd)

Active-Site Hydration and Water Diffusion in Cytochrome P450cam: A Highly Dynamic Process

Yinglong Miao, Jerome Baudry [University of Tennessee-Knoxville]

Biophysical Journal. **101**, 1493-1503, 2011.

Long-timescale molecular dynamics simulations (300 ns) are performed on both the apo- (i.e., camphor-free) and camphor-bound cytochrome P450cam (CYP101). Water diffusion into and out of the protein active site is observed without biased sampling methods. During the course of the molecular dynamics simulation, an average of 6.4 water molecules is observed in the camphor-binding site of the apo form, compared to zero water molecules in the binding site of the substrate-bound form, in agreement with the number of water molecules observed in crystal structures of the same species.

Dynamic Role of Cross-Linking Proteins in Actin Rheology

Taeyoon Kim, Wonmuk Hwang, Roger D. Kamm [Massachusetts Institute of Technology]

Biophysical Journal. **101**, 1597-1603, 2011.

We develop a computational model to compare the relative importance of unbinding and unfolding of actin cross-linking proteins (ACPs) in the dynamic properties of the actin cytoskeleton. We show that in the strain-stiffening regime with typical physiological and experimental strain rates, unbinding events are predominant with negligible unfolding. ACPs unbound by greater forces experience larger displacements, with a tendency to rebind to different filaments.

Protein interactions with surfaces: Computational approaches and repellency

Luisa Mayorga Szott, Thomas A Horbett [University of Washington, Seattle]

Curr. Opin. Chem. Biol., **15**, 683-689, 2011.

Study of protein adsorption to solid surfaces continues to be substantial because of its role in cellular responses to biomaterials, interest in molecular aspects such as conformation and orientation, new methods for making protein repellent surfaces, and new application areas such as nanoparticles and microfluidics. This brief review is based only on very recent articles of particular interest to the authors, who each have worked in this area for some time.

Can molecular dynamics simulations assist in design of specific inhibitors and imaging agents of amyloid aggregation? Structure, stability and free energy predictions for amyloid oligomers of VQIVYK, MVGGVV and LYQLEN

Workalemahu Mikre Berhanu and Artëm E. Masunov [University of Central Florida]

J. Mol.Mod., **17**, 2423-2442, 2011.

The aggregation modes of hexapeptide fragments of Tau, Insulin and A β peptide (VQIVYK, MVGGVV and LYQLEN) were found from their microcrystalline structures that had been recently resolved by X-ray analysis. The atomic structures reveal a dry self-complementary interface between the neighboring β -sheet layers, termed "steric zipper". In this study we perform several all-atom molecular dynamics simulations with explicit water to analyze stability of the crystalline fragments of 2-10 hexapeptides each and their analogs with single glycine replacement mutations to investigate the structural stability, aggregation behavior and thermodynamic of the amyloid oligomers.

Protein Dynamics (Cont'd)

The effect of a Pro28Thr point mutation on the local structure and stability of human galactokinase enzyme—a theoretical study

Balázs Jójárt [University of Szeged], Milán Szőri, Róbert Izsák, István Marsi and Aranka László, et al.

J. Mol.Mod., **17**, 2639-2649, 2011.

Galactokinase is responsible for the phosphorylation of α -D-galactose, which is an important step in the metabolism of the latter. Malfunctioning of galactokinase due to a single point mutation causes cataracts and, in serious cases, blindness. This paper reports a study of the Pro28Thr point mutation using a variety of theories including molecular dynamics (MD), MM-PBSA/GBSA calculations and AIM analysis. Altered H-bonding networks were detected based on geometric and electron density criteria that resulted in local unfolding of the β -sheet secondary structure.

A comparative study of HIV-1 and HTLV-I protease structure and dynamics reveals a conserved residue interaction network

Pia Rücker, Anselm H. C. Horn, Heike Meiselbach and Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J. Mol.Mod., **17**, 2693-2705, 2011.

The two retroviruses human T-lymphotropic virus type I (HTLV-I) and human immunodeficiency virus type 1 (HIV-1) are the causative agents of severe and fatal diseases. The retroviral proteases from HIV-1 and HTLV-I share 31% sequence identity and high structural similarities. Yet, their substrate specificities and inhibition profiles differ substantially. In this study, we performed all-atom MD simulations for both enzymes in their ligand-free states and in complex with model substrates in order to compare their dynamic behaviors and enhance our understanding of the correlation between sequence, structure, and dynamics in this protein family.

Self-Assembly of Semiflexible Homopolymers into Helical Bundles: A Brownian Dynamics Simulation Study

Tongtao Yue and Xianren Zhang [Beijing University of Chemical Technology]

J. Phys. Chem. B., **115**, 11566–11574, 2011.

The controllable self-assembly of semiflexible homopolymers into regular bundles has received much attention because of its potential importance in various fields, such as the storage of elastic energy, the fabrication of nanostructures, and the formation of the cytoskeleton in living cells. In this article, using computer simulations, we investigate how semiflexible homopolymers anchored on a substrate self-organize into ordered structures, focusing on both the patterns formed and the dynamics of self-assembly.

Understanding the Synergistic Effect of Arginine and Glutamic Acid Mixtures on Protein Solubility

Diwakar Shukla and Bernhardt L. Trout [Massachusetts Institute of Technology]

J. Phys. Chem. B., **115**, 11831–11839, 2011.

Understanding protein solubility is a key part of physical chemistry. In particular, solution conditions can have a major effect, and the effect of multiple cosolutes is little understood. It has been shown that the simultaneous addition of l-arginine hydrochloride and l-glutamic acid enhances the maximum achievable solubility of several poorly soluble proteins up to 4–8 times and reduces the intermolecular interactions between proteins. In this study, we have established the molecular mechanism behind this observed synergistic effect of arginine and glutamic acid mixtures using preferential interaction theory and molecular dynamics simulations of *Drosophila* Su(dx) protein (ww34).

Protein Dynamics (Cont'd)

Effects of the Val211Gly substitution on molecular dynamics of the CMY-2 cephalosporinase: Implications on hydrolysis of expanded-spectrum cephalosporins

Stathis D. Kotsakis, Leonidas S. Tzouveleakis, Efthymia Petinaki, Eva Tzelepi and Vivi Miriagou [Vivi Miriagou]

Proteins: Stru. Fun. and Bioinfo. **79**, 3180–3192, 2011.

CMY-30, a naturally occurring class C β -lactamase differing from the *Citrobacter freundii*-derived CMY-2 by a Val211Gly substitution in the Ω -loop, exhibits increased hydrolytic efficiency against ceftazidime and cefotaxime. Kinetic constants of CMY-2 and CMY-30 against the latter substrates suggested that the improved efficiency of the Gly211 variant was due to an increase in k_{cat} . The structural basis of the increased turn-over rates of oxyimino-cephalosporins caused by Val211Gly was studied using 5 ns MD simulations of CMY-2 and CMY-30 in their free forms and in covalent complexes with ceftazidime as well as a boronic acid analogue of ceftazidime.

Simulation of the β - to α -sheet transition results in a twisted sheet for antiparallel and an α -nanotube for parallel strands: Implications for amyloid formation

Steven Hayward [University of East Anglia] and E. James Milner-White

Proteins: Stru. Fun. and Bioinfo. **79**, 3193–3207, 2011

α -sheet has been proposed to be the main constituent of the toxic amyloid intermediate. Molecular dynamics simulations on proteins known to be involved in amyloid diseases have demonstrated that β -sheet can, under certain conditions, spontaneously convert to α -sheet via $\beta\beta \rightarrow \alpha_R\alpha_L$ peptide-plane flipping. Using torsion-angle driving to simulate this flip the transition has been investigated for parallel and antiparallel sheets. Concerted and sequential flipping processes were simulated, the former allowing direct calculation of helical parameters.

Free Energy Calculations

Accurate prediction of the enthalpies of formation for xanthophylls

Jenn-Huei Lii, Fu-Xing Liao and Ching-Han Hu [National Changhua University of Education]

J. Comp. Chem. **32**, 3175–3187, 2011.

This study investigates the applications of computational approaches in the prediction of enthalpies of formation (ΔH_f) for C-, H-, and O-containing compounds. Molecular mechanics (MM4) molecular mechanics method, density functional theory (DFT) combined with the atomic equivalent (AE) and group equivalent (GE) schemes, and DFT-based correlation corrected atomization (CCAZ) were used. We emphasized on the application to xanthophylls, C-, H-, and O-containing carotenoids which consist of ~ 100 atoms and extended π -delocalization systems.

Fast and accurate computation schemes for evaluating vibrational entropy of proteins

Beisi Xu, Hujun Shen, Xiao Zhu and Guohui Li [The Chinese Academy of Sciences]

J. Comp. Chem. **32**, 3188–3193, 2011.

Standard normal mode analysis (NMA) method is able to calculate vibrational entropy of proteins, but it is computationally intensive, especially for large proteins. To evaluate vibrational entropy efficiently and accurately, we, here, propose computation schemes based on coarse-grained NMA methods. This can be achieved by rescaling coarse-grained results with a specific factor that is derived on the basis of the linear correlation of protein vibrational entropy between standard NMA and coarse-grained NMA.

Free Energy Calculations (Cont'd)

Elucidating the Energetics of Entropically Driven Protein–Ligand Association: Calculations of Absolute Binding Free Energy and Entropy

Nan-jie Deng [The State University of New Jersey], Peng Zhang, Piotr Cieplak, and Luhua Lai

J. Phys. Chem. B., **115**, 11902–11910, 2011.

The binding of proteins and ligands is generally associated with the loss of translational, rotational, and conformational entropy. In many cases, however, the net entropy change due to binding is positive. To develop a deeper understanding of the energetics of entropically driven protein–ligand binding, we calculated the absolute binding free energies and binding entropies for two HIV-1 protease inhibitors Nelfinavir and Amprenavir using the double-decoupling method with molecular dynamics simulations in explicit solvent.

Ligand Binding/Docking

Preferential Binding of Peptides to Graphene Edges and Planes

Sang N. Kim, Zhifeng Kuang, Joseph M. Slocik, Sharon E. Jones, Yue Cui, Barry L. Farmer, Michael C. McAlpine, and Rajesh R. Naik [Wright-Patterson Air Force Base]

J. Am. Chem. Soc., **133**, 14480–14483, 2011.

Peptides identified from combinatorial peptide libraries have been shown to bind to a variety of abiotic surfaces. Biotic–abiotic interactions can be exploited to create hybrid materials with interesting electronic, optical, or catalytic properties. Here we show that peptides identified from a combinatorial phage display peptide library assemble preferentially to the edge or planar surface of graphene and can affect the electronic properties of graphene. Molecular dynamics simulations and experiments provide insight into the mechanism of peptide binding to the graphene edge.

A molecular dynamics study on opioid activities of biphalin molecule

Jin-Yuan Hsieh, Tzen-Yuh Chiang, Jun-Liang Chen, Chi-Chuan Hwang [National Cheng Kung University], Yun-Wen Chen and Hong-Chang Lin, et al.

J. Mol.Mod., **17**, 2455-2464, 2011.

MD simulations of the biphalin molecule, (Tyr-D-Ala-Gly-Phe-NH)₂, and the active tetrapeptide hydrazide, Tyr-D-Ala-Gly-Phe-NH-NH₂ were performed to investigate the cause of the increased μ and δ receptor binding affinities of the former over the latter. The simulation results demonstrate that the acylation of the two equal tetrapeptide fragments of biphalin produces the constrained hydrazide bridges C4–C4–N9–N10 and N9–N10–C5–C5, which in turn increase the opportunity of conformations for binding to μ or δ receptors.

Insights into binding modes of 5-HT_{2c} receptor antagonists with ligand-based and receptor-based methods

Chunhua Lu, Fangfang Jin, Cui Li, Weihua Li and Guixia Liu [East China University of Science and Technology], et al.

J. Mol.Mod., **17**, 2513-2523, 2011.

5-hydroxytryptamine-2c (5-HT_{2c}) receptor antagonists have clinical utility in the management of nervous system. In this work, ligand-based and receptor-based methods were used to investigate the binding mode of h5-HT_{2c} receptor antagonists. First, the pharmacophore modeling of the h5-HT_{2c} receptor antagonists was carried out by CATALYST. Then, the h5-HT_{2c} antagonists were docked to the h5-HT_{2c} receptor model. Subsequently, the comprehensive analysis of the pharmacophore and docking results revealed the structure-activity relationship of 5-HT_{2c} receptor antagonists and the key residues involved in the interactions.

Enzyme Catalysis

Enzyme Closure and Nucleotide Binding Structurally Lock Guanylate Kinase

Olivier Delalande, Sophie Sacquin-Mora, Marc Baaden
[Université Paris Diderot]

Biophysical Journal. **101**, 1440–1449, 2011.

We investigate the conformational dynamics and mechanical properties of guanylate kinase (GK) using a multiscale approach combining high-resolution atomistic molecular dynamics and low-resolution Brownian dynamics simulations. The GK enzyme is subject to large conformational changes, leading from an open to a closed form, which are further influenced by the presence of nucleotides. As suggested by recent work on simple coarse-grained models of apo-GK, we primarily focus on GK's closure mechanism with the aim to establish a detailed picture of the hierarchy and chronology of structural events essential for the enzymatic reaction.

Mechanism of Formation of the Internal Aldimine in Pyridoxal 5'-Phosphate-Dependent Enzymes

Eduardo F. Oliveira, Nuno M. F. S. A. Cerqueira, Pedro A. Fernandes, and Maria J. Ramos [Universidade do Porto]

J. Am. Chem. Soc., **133**, 15496–15505, 2011.

In this paper we studied the mechanism of formation of the internal aldimine, a common intermediate to most pyridoxal 5'-phosphate (PLP)-dependent enzymes. A large model based on the crystal structure from the human ornithine decarboxylase (ODC) enzyme was constructed and in total accounts for 504 atoms. The reaction mechanism was investigated using the ONIOM methodology (B3LYP/6-31G(d)//AM1), and the final energies were calculated with the M06/6-311++G(2d,2p)//B3LYP/6-31G(d) level of theory.

Human Butyrylcholinesterase–Cocaine Binding Pathway and Free Energy Profiles by Molecular Dynamics and Potential of Mean Force Simulations

Xiaoqin Huang, Fang Zheng, and Chang-Guo Zhan
[University of Kentucky]

J. Phys. Chem. B., **115**, 11254–11260, 2011.

In the present study, we have performed combined molecular dynamics and potential of mean force (PMF) simulations to determine the enzyme–substrate (ES) binding pathway and the corresponding free energy profiles for wild-type butyrylcholinesterase (BChE) binding with (–)/(+)-cocaine and for the A328W/Y332G mutant binding with (–)-cocaine. According to the PMF simulations, for each ES binding system, the substrate first binds with the enzyme at a peripheral anionic site around the entrance of the active-site gorge to form the first ES complex (ES1-like) during the binding process.

The Effects of Protein Environment and Dispersion on the Formation of Ferric-Superoxide Species in myo-Inositol Oxygenase (MIOX): A Combined ONIOM(DFT:MM) and Energy Decomposition Analysis

Hajime Hirao [Nanyang Technological University]

J. Phys. Chem. B., **115**, 11278–11285, 2011.

The catalytic reaction of myo-inositol oxygenase, a nonheme diiron enzyme, is initiated by the binding of an O₂ molecule to the ferrous center of a mixed-valence Fe(II)Fe(III) intermediate. This generates a (superoxo)Fe(III)Fe(III) reactive species that abstracts a hydrogen atom from the myo-inositol substrate. To understand the effects of protein environment and intracluster dispersion on this O₂-binding process, we undertook a combined ONIOM(B3LYP:AMBER) and energy decomposition analysis.

Protein-Protein Interactions

Enhancing systematic protein–protein docking methods using ray casting: Application to ATTRACT

Yi Li, Juan Cortés and Thierry Siméon [CNRS, LAAS]

Proteins: Stru. Fun. and Bioinfo. **79**, 3037–3049, 2011.

Systematic protein–protein docking methods need to evaluate a huge number of different probe configurations, thus leading to high computational cost. We present an efficient filter—ray casting filter (RCF)—that enables a notable speed-up of systematic protein–protein docking. The high efficiency of RCF is the outcome of the following factors: (i) extracting of pockets and protrusions on the surfaces of the proteins using visibilities; (ii) a ray casting method that finds aligned receptor pocket/probe protrusion pairs without explicit similarity computations.

Docking and free energy simulations to predict conformational domains involved in hCG–LH receptor interactions using recombinant antibodies

Ritankar Majumdar, Reema Railkar and Rajan R. Dighe [Indian Institute of Sciences, Bangalore]

Proteins: Stru. Fun. and Bioinfo. **79**, 3108–3122, 2011.

Single chain fragment variables (ScFvs) have been extensively employed in studying the protein–protein interactions. ScFvs derived from phage display libraries have an additional advantage of being generated against a native antigen, circumventing loss of information on conformational epitopes. In the present study, an attempt has been made to elucidate human chorionic gonadotropin (hCG)–luteinizing hormone (LH) receptor interactions by using a neutral and two inhibitory ScFvs against hCG. The objective was to dock a computationally derived model of these ScFvs onto the crystal structure of hCG and understand the differential roles of the mapped epitopes in hCG–LH receptor interactions.

Membrane Proteins and Lipid Peptide Interactions

Oxidized Phosphatidylcholines Facilitate Phospholipid Flip-Flop in Liposomes

Roman Volinsky, Lukasz Cwiklik, Piotr Jurkiewicz, Martin Hof, Pavel Jungwirth, Paavo K.J. Kinnunen [Aalto University]

Biophysical Journal. **101**, 1376–1384, 2011.

Lipid asymmetry is a ubiquitous property of the lipid bilayers in cellular membranes and its maintenance and loss play important roles in cell physiology, such as blood coagulation and apoptosis. A combination of fluorescence spectroscopy and molecular dynamics simulations reveal that the mechanistic basis for this property of oxidized phosphatidylcholines is due to major changes imposed by the oxidized phospholipids on the biophysical properties of lipid bilayers, resulting in a fast cross bilayer diffusion of membrane phospholipids and loss of lipid asymmetry, requiring no scramblase protein.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Structure of a protein–detergent complex: the balance between detergent cohesion and binding

Jonathan Khao, Jaime Arce-Lopera, James N. Sturgis and Jean-Pierre Duneau [CNRS—Aix Marseille Université]

Europ. Biophys. Jou., **40**, 1143–1155, 2011.

Despite the major interest in membrane proteins at functional, genomic, and therapeutic levels, their biochemical and structural study remains challenging, as they require, among other things, solubilization in detergent micelles. The complexity of this task derives from the dependence of membrane protein structure on their anisotropic environment, influenced by a delicate balance between many different physicochemical properties. To study such properties in a small protein–detergent complex, we used fluorescence measurements and MD simulations on the transmembrane part of glycophorin A (GpAtm) solubilized in micelles of dihexanoylphosphatidylcholine detergent.

A Molecular Mechanics Approach to Modeling Protein–Ligand Interactions: Relative Binding Affinities in Congeneric Series

Chaya Rapp, Chakrapani Kalyanaraman, Aviva Schiffmiller, Esther Leah Schoenbrun, and Matthew P. Jacobson [University of California San Francisco]

J.Chem. Infor. and Mod. **51**, 2082–2089, 2011.

We introduce the “Prime-ligand” method for ranking ligands in congeneric series. The method employs a single scoring function, the OPLS-AA/GBSA molecular mechanics/implicit solvent model, for all stages of sampling and scoring. We evaluate the method using 12 test sets of congeneric series for which experimental binding data is available in the literature, as well as the structure of one member of the series bound to the protein. Ligands are “docked” by superimposing a common stem fragment among the compounds in the series using a crystal complex from the Protein Data Bank and sampling the conformational space of the variable region.

Enhanced Lipid Diffusion and Mixing in Accelerated Molecular Dynamics

Yi Wang [University of California, San Diego], Phineus R. L. Markwick, César Augusto F. de Oliveira, and J. Andrew McCammon

J. Chem. Theor. and Comp., **7**, 3199–3207, 2011.

Accelerated molecular dynamics (aMD) is an enhanced sampling technique that expedites conformational space sampling by reducing the barriers separating various low-energy states of a system. Here, we present the first application of the aMD method on lipid membranes. Altogether, $\sim 1.5 \mu\text{s}$ simulations were performed on three systems: a pure POPC bilayer, a pure DMPC bilayer, and a mixed POPC:DMPC bilayer. Overall, the aMD simulations are found to produce significant speedup in trans–gauche isomerization and lipid lateral diffusion versus those in conventional MD (cMD) simulations.

Gating and Intermolecular Interactions in Ligand-Protein Association: Coarse-Grained Modeling of HIV-1 Protease

Myungshim Kang, Christopher Roberts, Yuhui Cheng, and Chia-en A. Chang [University of California, Riverside]

J. Chem. Theor. and Comp., **7**, 3438–3446, 2011.

Most biological processes are initiated or mediated by the association of ligands and proteins. This work studies multistep, ligand–protein association processes by Brownian dynamics simulations with coarse-grained models for HIV-1 protease (HIVp) and its neutral ligands. We report the average association times when the ligand concentration is $100 \mu\text{M}$. The influence of crowding on the simulated binding time was also studied. HIVp has flexible loops that serve as a gate during the ligand binding processes.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Atomistic Molecular Dynamics Simulations of the Interactions of Oleic and 2-Hydroxyoleic Acids with Phosphatidylcholine Bilayers

Javier Cerezo, José Zúñiga, Adolfo Bastida, and Alberto Requena, José Pedro Cerón-Carrasco [Universidad de Murcia]

J. Phys. Chem. B., **115**, 11727–11738, 2011.

Fatty oleic acid (OA) and, recently, its derivative 2-hydroxyoleic acid (2OHOA) have been reported to display an important therapeutic activity. To understand better these therapeutic effects at the molecular and cellular levels, in this work we have carried out molecular dynamics simulations to elucidate the structural and dynamical changes taking place in model 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) bilayers upon insertion of rising concentrations of these two fatty acids. The simulations are performed using a united-atoms model to describe both the phospholipids and the fatty acids.

Protein Folding

Improvement of Structure-Based Potentials for Protein Folding by Native and Nonnative Hydrogen Bonds

Marta Enciso, Antonio Rey [Universidad Complutense]

Biophysical Journal. **101**, 1474-1482, 2011.

Pure Gō models (where every native interaction equally stabilizes the folded state) have widely proved their convenience in the computational investigation of protein folding. Among all the noncovalent interactions that contribute to protein folding, hydrogen bonds are the only ones with a partial covalent character. We show that the explicit inclusion of hydrogen bonds leads to a systematic improvement in the description of protein folding.

Three Force Fields' Views of the 3_{10} Helix

Kalliopi K. Patapati, Nicholas M. Glykos [Democritus University of Thrace]

Biophysical Journal. **101**, 1766-1771, 2011.

Slowly but steadily bibliographic evidence is accumulating that the apparent convergence of the various biomolecular force fields as evidenced from simulations of proteins in the folded state does not hold true for folding simulations. Here we add one more example to the growing list of peptides and proteins for which different force fields show irreconcilable differences in their folding predictions, even at such a fundamental level as that of a peptide's secondary structure. We show that for an undecamer peptide that is known from two independent NMR structure determinations to have a mainly 3_{10} -helical structure in solution, three mainstream biomolecular force fields give completely disparate predictions.

Protein Folding (Cont'd)

Simulation Studies of Protein Folding/Unfolding Equilibrium under Polar and Nonpolar Confinement

Jianhui Tian and Angel E. Garcia [Rensselaer Polytechnic Institute, Troy]

J. Am. Chem. Soc., **133**, 15157–15164, 2011.

We study the equilibrium folding/unfolding thermodynamics of a small globular miniprotein, the Trp cage, that is confined to the interior of a 2 nm radius fullerene ball. The interactions of the fullerene surface are changed from nonpolar to polar to mimic the interior of the GroEL/ES chaperonin that assists proteins to fold in vivo. We find that nonpolar confinement stabilizes the folded state of the protein due to the effects of volume reduction that destabilize the unfolded state and also due to interactions with the fullerene surface.

A New Two-State Polymer Folding Model and Its Application to α -Helical Polyalanine

Per Linse [Lund University], Peter Palenčár, and Tomáš Bleha

J. Phys. Chem. B., **115**, 11448–11454, 2011.

A new two-state polymer folding model is proposed, in which the folding of a stiff helical polymer is enabled by allowing for short sequences of coils connecting shorter and separated helices. The folding is driven by short-range attraction energy among stacked helices and is opposed by the free-energy cost of forming coils from helical monomers. Principal outcomes of the model are equilibrium distribution of the number of helices and their length in helical polymers.

Analysis of Infrared Spectra of β -Hairpin Peptides As Derived from Molecular Dynamics Simulations

Laura Zanetti Polzi, Isabella Daidone, Massimiliano Anselmi, Giuliano Carchini, Alfredo Di Nola, and Andrea Amadei [University of Rome “Tor Vergata”]

J. Phys. Chem. B., **115**, 11872–11878, 2011.

Infrared temperature-dependent spectroscopy is a well-known tool to characterize folding/unfolding transitions in peptides and proteins, assuming that the higher the temperature, the higher the unfolded population. The infrared spectra at different temperatures of two β -hairpin peptides (gramicidin S analogues GS6 and GS10) are here reconstructed by means of molecular dynamics (MD) simulations and a theoretical-computational method based on the perturbed matrix method. The calculated temperature-dependent spectra result in good agreement with the experimental available spectra.

Nucleic Acids

Structural Rigidity of Paranemic Crossover and Juxtapose DNA Nanostructures

Mogurampelly Santosh, Prabal K. Maiti [Indian Institute of Science, Bangalore]

Biophysical Journal. **101**, 1393–1402, 2011.

Crossover motifs are integral components for designing DNA-based nanostructures and nanomechanical devices due to their enhanced rigidity compared to the normal B-DNA. We have used fully atomistic molecular dynamics simulations in explicit solvent to get the force-extension curve of parallel DNA nanostructures to characterize their mechanical rigidity. In the presence of monovalent Na^+ ions, we find that the stretch modulus (γ_1) of the paranemic crossover and its topoisomer JX DNA structure is significantly higher (~30%) compared to normal B-DNA of the same sequence and length.

Nucleic Acids (Cont'd)

Unlinking of Supercoiled DNA Catenanes by Type IIA Topoisomerases

Alexander Vologodskii [New York University]

Biophysical Journal. **101**, 1403-1411, 2011.

It was found recently that DNA catenanes, formed during replication of circular plasmids, become positively (+) supercoiled, and the unlinking of such catenanes by type IIA topoisomerases proceeds much more efficiently than the unlinking of negatively (–) supercoiled catenanes. In an attempt to explain this striking finding we studied, by computer simulation, conformational properties of supercoiled DNA catenanes.

Dynamical Allostery in the Mechanism of Action of DNA Mismatch Repair Protein MutS

Susan N. Pieniazek [Wesleyan University], Manju M. Hingorani, D.L. Beveridge

Biophysical Journal. **101**, 1730-1739, 2011.

The multidomain protein *Thermus aquaticus* MutS and its prokaryotic and eukaryotic homologs recognize DNA replication errors and initiate mismatch repair. MutS actions are fueled by ATP binding and hydrolysis, which modulate its interactions with DNA and other proteins in the mismatch-repair pathway. The DNA binding and ATPase activities are allosterically coupled over a distance of ~70 Å, and the molecular mechanism of coupling has not been clarified. To address this problem, all-atom molecular dynamics simulations of ~150 ns including explicit solvent were performed on two key complexes—ATP-bound and ATP-free MutS·DNA(+T bulge).

Spectroscopic Detection of DNA Quadruplexes by Vibrational Circular Dichroism

Valery Andrushchenko, Dimiter Tsankov, Maria Krasteva, Helmut Wieser, and Petr Bour [Academy of Sciences of the Czech Republic]

J. Am. Chem. Soc., **133**, 15055–15064, 2011.

The four-stranded G-quadruplex motif is a conformation frequently adopted by guanine-rich nucleic acids that plays an important role in biology, medicine, and nanotechnology. Although vibrational spectroscopy has been widely used to investigate nucleic acid structure, association of particular spectral features with the quadruplex structure has to date been ambiguous. In this work, experimental IR absorption and vibrational circular dichroism (VCD) spectra of the model quadruplex systems d(G)₈ and deoxyguanosine-5'-monophosphate (5'-dGMP) were analyzed using molecular dynamics (MD) and quantum-chemical modeling.

Modeling the Chemical Step Utilized by Human Alkyladenine DNA Glycosylase: A Concerted Mechanism Aids in Selectively Excising Damaged Purines

Lesley R. Rutledge and Stacey D. Wetmore [University of Lethbridge]

J. Am. Chem. Soc., **133**, 16258–16269, 2011.

Human alkyladenine DNA glycosylase (AAG) initiates the repair of a wide variety of (neutral or cationic) alkylated and deaminated purines by flipping damaged nucleotides out of the DNA helix and catalyzing the hydrolytic N-glycosidic bond cleavage. Detailed ONIOM(M06-2X/6-31G(d):AMBER) reaction potential energy surface scans are used to gain the first atomistic perspective of the repair pathway used by AAG.

Nucleic Acids (Cont'd)

Evaluation of DNA Force Fields in Implicit Solvation

Thomas Gaillard and David A. Case [Rutgers—The State University of New Jersey]

J. Chem. Theor. and Comp., **7**, 3181–3198, 2011.

DNA structural deformations and dynamics are crucial to its interactions in the cell. Theoretical simulations are essential tools used to explore the structure, dynamics, and thermodynamics of biomolecules in a systematic way. Molecular mechanics force fields for DNA have benefited from constant improvements during the past decades. In this study, respective influences of the force field and the implicit solvation model choice on DNA simulation quality are evaluated.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Modeling the molecular basis for $\alpha 4\beta 1$ integrin antagonism

Oliver E. Hutt, Simon Saubern, David A. Winkler [CSIRO Materials Science and Engineering]

Bioorg. and Med.Chem., **19**, 5903-5911, 2011.

We report a 3D QSAR study of almost 300 structurally diverse small molecule antagonists of the integrin $\alpha 4\beta 1$ whose biological activity spans six orders of magnitude. The alignment of the molecules was based on the conformation of a structurally related ligand bound to the $\alpha IIB\beta 3$ and $\alpha v\beta 3$ integrins in X-ray crystallographic studies. The molecular field method, CoMSIA, was used to generate the 3D QSAR models. The resulting models showed that the lipophilic properties were the most important, with hydrogen bond donor and steric properties less relevant.

Three-dimensional quantitative structure–activity relationship analyses of substrates of the human proton-coupled amino acid transporter 1 (hPAT1)

Iris Thondorf [Martin-Luther-University Halle-Wittenberg], Valerie Voigt, Sarah Schäfer, Sabine Gebauer, Katja Zebisch, Linda Laug, Matthias Brandsch

Bioorg. and Med.Chem., **19**, 6409-6418, 2011.

The proton-coupled amino acid transporter hPAT1 has recently gained much interest due to its ability to transport small drugs thereby allowing their oral administration. A three-dimensional quantitative structure–activity relationship (3D QSAR) study has been performed on its natural and synthetic substrates employing comparative molecular similarity indices analysis (CoMSIA) to investigate the structural requirements for substrates and to derive a predictive model that may be used for the design of new prodrugs.

Zinc–Homocysteine binding in cobalamin-dependent methionine synthase and its role in the substrate activation: DFT, ONIOM, and QM/MM molecular dynamics studies

Safwat Abdel-Azeim, Xin Li, Lung Wa Chung and Keiji Morokuma [Kyoto University]

J. Comp. Chem. **32**, 3154–3167, 2011.

Cobalamin-dependent methionine synthase (MetH) is an important metalloenzyme responsible for the biosynthesis of methionine. It catalyzes methyl transfer from N⁵-methyl-tetrahydrofolate to homocysteine (Hcy) by using a zinc ion to activate the Hcy substrate. Density functional theory (B3LYP) calculations on the active-site model in gas phase and in a polarized continuum model were performed to study the Zn coordination changes from the substrate-unbound state to the substrate-bound state. The protein effect on the Zn²⁺ coordination exchange was further investigated by ONIOM (B3LYP:AMBER)-ME and EE calculations.

Quantitative Structure-Activity Relations (Cont'd)

Novel Peptide-Specific Quantitative Structure-Activity Relationship (QSAR) Analysis Applied to Collagen IV Peptides with Antiangiogenic Activity

Corban G. Rivera [Johns Hopkins University], Elena V. Rosca, Niranjan B. Pandey, Jacob E. Koskimaki, Joel S. Bader, and Aleksander S. Popel

J. Med. Chem. **54**, 6492–6500, 2011.

Angiogenesis is the growth of new blood vessels from existing vasculature. Excessive vascularization is associated with a number of diseases including cancer. Antiangiogenic therapies have the potential to stunt cancer progression. Peptides derived from type IV collagen are potent inhibitors of angiogenesis. We wanted to gain a better understanding of collagen IV structure-activity relationships using a ligand-based approach. We developed novel peptide-specific QSAR models to study the activity of the peptides in endothelial cell proliferation, migration, and adhesion inhibition assays.

Potentials and Parameters

CHARMM Additive All-Atom Force Field for Carbohydrate Derivatives and Its Utility in Polysaccharide and Carbohydrate-Protein Modeling

Olgun Guvench, Sairam S. Mallajosyula, E. Prabhu Raman, Elizabeth Hatcher, Kenno Vanommeslaeghe, Theresa J. Foster, Francis W. Jamison, II, and Alexander D. MacKerell, Jr. [University of Maryland School of Pharmacy]

J. Chem. Theor. and Comp. **7**, 3162–3180, 2011.

Monosaccharide derivatives such as xylose, fucose, N-acetylglucosamine (GlcNAc), N-acetylgalactosamine (GlaNAc), glucuronic acid, iduronic acid, and N-acetylneuraminic acid (Neu5Ac) are important components of eukaryotic glycans. The present work details the development of force-field parameters for these monosaccharides and their covalent connections to proteins via O linkages to serine or threonine side chains and via N linkages to asparagine side chains. The force field development protocol was designed to explicitly yield parameters that are compatible with the existing CHARMM additive force field for proteins, nucleic acids, lipids, carbohydrates, and small molecules.

How T cell receptors interact with peptide-MHCs: A multiple steered molecular dynamics study

Michel A. Cuendet, Vincent Zoete and Olivier Michielin [Swiss Institute of Bioinformatics]

Proteins: Stru. Fun. and Bioinfo. **79**, 3007–3024, 2011.

The T-cell receptor (TCR) interaction with antigenic peptides (p) presented by the major histocompatibility complex (MHC) molecule is a key determinant of immune response. In addition, TCR-pMHC interactions offer examples of features more generally pertaining to protein-protein recognition: subtle specificity and cross-reactivity. In this study, we perform extensive equilibrium and steered molecular dynamics simulations to study the unbinding of three TCR-pMHC complexes.

Solvation Energy

Soft-core potentials in thermodynamic integration: Comparing one- and two-step transformations

Thomas Steinbrecher [Universität Karlsruhe], InSuk Joung and David A. Case

J. Comp. Chem. **32**, 3253–3263, 2011.

Molecular dynamics-based free energy calculations allow the determination of a variety of thermodynamic quantities from computer simulations of small molecules. Thermodynamic integration (TI) calculations can suffer from instabilities during the creation or annihilation of particles. “one-step” transformations, in which electrostatic and van der Waals forces are simultaneously modified, can be simpler and less expensive than “two-step” transformations in which these properties are changed in separate calculations. Here, we study solvation free energies for molecules of different hydrophobicity using both models.

Molecular Dynamics

Motion of a Disordered Polypeptide Chain as Studied by Paramagnetic Relaxation Enhancements, ^{15}N Relaxation, and Molecular Dynamics Simulations: How Fast Is Segmental Diffusion in Denatured Ubiquitin?

Yi Xue and Nikolai R. Skrynnikov [Purdue University]

J. Am. Chem. Soc., **133**, 14614–14628, 2011.

Molecular dynamics (MD) simulations have been widely used to analyze dynamic conformational equilibria of folded proteins, especially in relation to NMR observables. However, this approach found little use in the studies of disordered proteins, where the sampling of vast conformational space presents a serious problem. In this paper, we demonstrate that the latest advances in computation technology make it possible to overcome this limitation. The experimentally validated (calibrated) MD models allow for new insights into structure/dynamics of disordered proteins.

Trajectory NG: portable, compressed, general molecular dynamics trajectories

Daniel Spångberg [Uppsala University], Daniel S. D. Larsson and David van der Spoel

J. Mol. Mod., **17**, 2669–2685, 2011.

We present general algorithms for the compression of molecular dynamics trajectories. The standard ways to store MD trajectories as text or as raw binary floating point numbers result in very large files when efficient simulation programs are used on supercomputers. Our algorithms are based on the observation that differences in atomic coordinates/velocities, in either time or space, are generally smaller than the absolute values of the coordinates/velocities. Also, it is often possible to store values at a lower precision. We apply several compression schemes to compress the resulting differences further.

Recursive Taylor Series Expansion Method for Rigid-Body Molecular Dynamics

Alexey V. Akimov [Rice University, Houston] and Anatoly B. Kolomeisky

J. Chem. Theor. and Comp., **7**, 3062–3071, 2011.

Molecular dynamics computer simulation methods are very important for understanding mechanisms of chemical, physical, and biological processes. The reliability of molecular dynamics simulations strongly depends on the integration schemes used in the simulations. In this work, we developed new rigid body integration schemes for molecular dynamics simulations. Our approach is based on a numerically exact solution to the free rigid body problem, which is used in the classical propagator splitting scheme.

Molecular Dynamics (Cont'd)

MSMBuilder2: Modeling Conformational Dynamics on the Picosecond to Millisecond Scale

Kyle A. Beauchamp, Gregory R. Bowman, Thomas J. Lane, Lutz Maibaum, Imran S. Haque, and Vijay S. Pande [Stanford University]

J. Chem. Theor. and Comp., **7**, 3412–3419, 2011.

Markov state models provide a framework for understanding the fundamental states and rates in the conformational dynamics of biomolecules. We describe an improved protocol for constructing Markov state models from molecular dynamics simulations. The new protocol includes advances in clustering, data preparation, and model estimation; these improvements lead to significant increases in model accuracy, as assessed by the ability to recapitulate equilibrium and kinetic properties of reference systems.

Molecular Insight into Conformational Transition of Amyloid β -Peptide 42 Inhibited by (–)-Epigallocatechin-3-gallate Probed by Molecular Simulations

Fu-Feng Liu, Xiao-Yan Dong, Lizhong He, Anton P. J. Middelberg, and Yan Sun [Tianjin University]

J. Phys. Chem. B., **115**, 11879–11887, 2011.

Considerable experimental evidence indicates that (–)-epigallocatechin-3-gallate (EGCG) inhibits the fibrillogenesis of $A\beta_{42}$ and alleviates its associated cytotoxicity. However, the molecular mechanism of the inhibition effect of EGCG on the conformational transition of $A\beta_{42}$ remains unclear due to the limitations of current experimental techniques. In this work, molecular dynamics simulations and molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) analysis were coupled to better understand the issue. It was found that the direct interactions between EGCG and the peptide are the origin of its inhibition effects.

Exploration of Transferability in Multiscale Coarse-Grained Peptide Models

Ian F. Thorpe, David P. Goldenberg, and Gregory A. Voth [University of Utah]

J. Phys. Chem. B., **115**, 11911–11926, 2011.

Coarse-grained models can facilitate the efficient simulation of complex biological systems. In earlier studies the multiscale coarse-graining (MS-CG) method was employed to examine the folding landscape for two small peptides. In those studies, MS-CG force fields specific to each peptide were employed. We extend here the scope of that work with the goal of obtaining a transferable MS-CG force field which can be used to simulate the folded conformations of peptides with disparate structural motifs.

Monte Carlo

Molecular Monte Carlo Simulations Using Graphics Processing Units: To Waste Recycle or Not?

Jihan Kim [Lawrence Berkeley National Laboratory, Berkeley], Jocelyn M. Rodgers, Manuel Athènes, and Berend Smit

J. Chem. Theor. and Comp., **7**, 3208–3222, 2011.

In the waste recycling Monte Carlo (WRMC) algorithm,⁽¹⁾ multiple trial states may be simultaneously generated and utilized during Monte Carlo moves to improve the statistical accuracy of the simulations, suggesting that such an algorithm may be well posed for implementation in parallel on graphics processing units (GPUs). In this paper, we implement two waste recycling Monte Carlo algorithms in CUDA (Compute Unified Device Architecture) using uniformly distributed random trial states and trial states based on displacement random-walk steps, and we test the methods on a methane-zeolite MFI framework system to evaluate their utility.

QM and QM/MM

Proton Storage Site in Bacteriorhodopsin: New Insights from Quantum Mechanics/Molecular Mechanics Simulations of Microscopic pK_a and Infrared Spectra

Puja Goyal, Nilanjan Ghosh, Prasad Phatak, Maike Clemens, Michael Gaus, Marcus Elstner, and Qiang Cui [University of Wisconsin, Madison]

J. Am. Chem. Soc., **133**, 14981–14997, 2011.

Identifying the group that acts as the proton storage/loading site is a challenging but important problem for understanding the mechanism of proton pumping in biomolecular proton pumps, such as bacteriorhodopsin (bR) and cytochrome c oxidase. Recent experimental studies of bR propelled the idea that the proton storage/release group (PRG) in bR is not an amino acid but a water cluster embedded in the protein. We argue that this idea is at odds with our knowledge of protein electrostatics. Our recent QM/MM simulations suggested an alternative “intermolecular proton bond” model in which the stored proton is shared between two conserved Glu residues (194 and 204).

In silico evaluation of proposed biosynthetic pathways for the unique dithiolate ligand of the H-cluster of [FeFe]-hydrogenase

Alexios Grigoropoulos and Robert K. Szilagyi [Montana State University]

J. Comp. Chem. **32**, 3194–3206, 2011.

The biosynthesis of the active site of the [FeFe]-hydrogenases (H-cluster) remains a tantalizing puzzle due to its unprecedented and complex ligand environment. Various experimentally testable hypotheses have already been put forward regarding the precursor molecule and the biosynthetic mechanism that leads to the formation of the dithiolate ligand. In this work, we report a density functional theory-based theoretical evaluation of these hypotheses.

Role of physicochemical properties in the activation of peroxisome proliferator-activated receptor δ

Vinícius G. Maltarollo, Paula Homem-de-Mello and Káthia M. Honório [Universidade Federal do ABC]

J. Mol.Mod., **17**, 2549-2558, 2011.

Current researches on treatments for metabolic diseases involve a class of biological receptors called peroxisome proliferator-activated receptors (PPARs), which control the metabolism of carbohydrates and lipids. A subclass of these receptors, PPAR δ , regulates several metabolic processes, and the substances that activate them are being studied as new drug candidates for the treatment of diabetes mellitus and metabolic syndrome. In this study, several PPAR δ agonists with experimental biological activity were selected for a structural and chemical study.

Mechanistic study of the structure–activity relationship for the free radical scavenging activity of baicalein

Zoran S. Marković, Jasmina M. Dimitrić Marković [University of Belgrade], Dejan Milenković and Nenad Filipović

J. Mol.Mod., **17**, 2575-2584, 2011.

Density functional theory calculations were performed to evaluate the antioxidant activity of baicalein. The conformational behaviors of both the isolated and the aqueous-solvated species (simulated with the conductor-like polarizable continuum solvation model) were analyzed at the M052X/6-311++G(d,p) level. The most stable tautomers of various forms of baicalein displayed three IHBs between O4 and OH5, O5 and OH6, and O6 and OH7. The most stable tautomer of the baicalein radical was obtained by dehydrogenating the hydroxyl at C6, while the most stable anion tautomer was obtained by deprotonating the C7 hydroxyl in gaseous and aqueous phases.

QM and QM/MM (Cont'd)

Hydrogen bonding interactions in noradrenaline-DMSO complexes: DFT and QTAIM studies of structure, properties and topology

Zhengguo Huang [Tianjin Normal University], Yumei Dai, Lei Yu and Hongke Wang

J. Mol.Mod., **17**, 2609-2621, 2011.

The hydrogen bonding interactions between noradrenaline (NA) and DMSO were studied with density functional theory (DFT) regarding their geometries, energies, vibrational frequencies, and topological features of the electron density. The quantum theory of atoms in molecules (QTAIM) and the natural bond orbital (NBO) analyses were employed to elucidate the hydrogen bonding interaction characteristics in noradrenaline-DMSO complexes. The H-bonds involving the hydroxyls hydrogen in NA and the O atom in DMSO are dominant intermolecular H-bonds and are stronger than other H-bonds involving the methyl hydrogen of DMSO as a H-donor.

DFT and MP2 investigations of L-proline and its hydrated complexes

Xiao-Jun Li [Weinan Teachers University], Zhi-Jian Zhong and Hai-Zhen Wu

J. Mol.Mod., **17**, 2623-2630, 2011.

A theoretical study of L-proline-nH₂O (n = 1–3) has been performed using the hybrid DFT-B3LYP and MP2 methods together with the 6-311++G(d,p) basis set. The results show that the P2 conformer is energetically favorable when forming a hydrated structure, and the hydration of the carboxyl group leads to the greatest stability. For hydrated complexes, the adiabatic and vertical singlet–triplet excitation energies tend to decrease with the addition of water molecules.

Computational analysis of aspartic protease plasmepsin II complexed with EH58 inhibitor: a QM/MM MD study

Natália de Farias Silva, Jerônimo Lameira and Cláudio Nahum Alves [Universidade Federal do Pará]

J. Mol.Mod., **17**, 2631-2638, 2011.

Plasmepsin (PM) II is one of four enzymes in the food vacuole of *Plasmodium falciparum*. It has become an attractive target for combating malaria through research regarding its importance in the *P. falciparum* metabolism and life cycle, making it the target of choice for structure-based drug design. This paper reports the results of hybrid QM/MM and MD simulations employed to study the details of the interactions established between PM II and N-(3-((2-benzo[1,3]dioxol-5-yl-ethyl)[3-(1-methyl-3-oxo-1,3-dihydro-isoindol-2-yl) propionyl]-amino)-1-benzyl-2-(hydroxyl-propyl)-4-benzyloxy-3,5-dimethoxy-benzamide (EH58), a well-known potent inhibitor for this enzyme.

Mechanism for the Autophosphorylation of CheA Histidine Kinase: QM/MM Calculations

Ting Shi, Yunxiang Lu, Xinyi Liu, Yingyi Chen, Hualiang Jiang, and Jian Zhang [Shanghai JiaoTong University School of Medicine]

J. Phys. Chem. B., **115**, 11895–11901, 2011.

The CheA histidine kinase, a model of TCS (the two-component system), mediates the signal transduction pathway of bacterial chemotaxis via autophosphorylation. Since the TCSs are rarely found in mammals, they have become attractive targets for the development of new antibiotics. To characterize the autophosphoryl-transfer mechanism of CheA histidine kinase, molecular dynamics simulations combined with quantum mechanics/molecular mechanics calculations were employed on the constructed 3D model of P1–P4–ATP complex.

Comparative or Homology Modeling

Ligand supported homology modeling and docking evaluation of CCR2: docked pose selection by consensus scoring

Jong-Hoon Kim [Yonsei University], Jee Woong Lim, Seung-Woo Lee, Kyoungrak Kim and Kyoung Tai No

J. Mol.Mod., **17**, 2707-2716, 2011.

Chemokine receptor 2 (CCR2) is a G-protein coupled receptor (GPCR) and a crucial target for various inflammatory and autoimmune diseases. Homology modeling is widely used for the study of GPCR-ligand binding. Since there is substantial diversity for the ligand binding pocket and binding modes among GPCRs, the receptor-ligand binding mode predictions should be derived from homology modeling with supported ligand information. Thus, we modeled the binding of our proprietary CCR2 antagonist using ligand supported homology modeling followed by consensus scoring the docking evaluation based on all modeled binding sites.

Antibody modeling assessment

Juan C. Almagro [Centocor R&D, Inc., (Johnson and Johnson)], Mary Pat Beavers, Francisco Hernandez-Guzman, Johannes Maier, Jodi Shaulsky, Kenneth Butenhof, Paul Labute, Nels Thorsteinson, Kenneth Kelly, Alexey Teplyakov, Jinquan Luo, Raymond Sweet and Gary L. Gilliland

Proteins: Stru. Fun. and Bioinfo. **79**, 3050–3066, 2011.

A blinded study to assess the state of the art in three-dimensional structure modeling of the variable region (Fv) of antibodies was conducted. Nine unpublished high-resolution x-ray Fab crystal structures covering a wide range of antigen-binding site conformations were used as benchmark to compare Fv models generated by four structure prediction methodologies. The methodologies included two homology modeling strategies independently developed by CCG and Accerlys Inc, and two fully automated antibody modeling servers: PIGS, based on the canonical structure model, and Rosetta Antibody Modeling, based on homology modeling and Rosetta structure prediction methodology.

Design of a modified mouse protein with ligand binding properties of its human analog by molecular dynamics simulations: The case of C3 inhibition by compstatin

Phanourios Tamamis, Panayiota Pierou, Chrystalla Mytidou, Christodoulos A. Floudas, Dimitrios Morikis [University of California] and Georgios Archontis

Proteins: Stru. Fun. and Bioinfo. **79**, 3166–3179, 2011.

The peptide compstatin and its derivatives inhibit the complement-component protein C3 in primate mammals and are potential therapeutic agents against the unregulated activation of complement in humans, but are inactive against C3 from lower mammals. Recent MD simulations showed that the most potent compstatin analog comprised entirely of natural amino acids (W4A9) had a smaller affinity for rat C3, due to reproducible changes in the rat protein structure with respect to the human protein, which eliminated or weakened specific protein–ligand interactions seen in the human C3:W4A9 complex. Here, we study by MD simulations three W4A9 complexes with the mouse C3 protein, and two “transgenic” mouse derivatives, containing a small number (6–9) of human C3 substitutions.

Ligand Docking

LigDockCSA: Protein–ligand docking using conformational space annealing

Woong-Hee Shin, Lim Heo, Juyong Lee, Junsu Ko, Chaok Seok [Seoul National University] and Jooyoung Lee

J. Comp. Chem. **32**, 3226–3232, 2011.

Protein–ligand docking techniques are one of the essential tools for structure-based drug design. Two major components of a successful docking program are an efficient search method and an accurate scoring function. In this work, a new docking method called LigDockCSA is developed by using a powerful global optimization technique, conformational space annealing (CSA), and a scoring function that combines the AutoDock energy and the piecewise linear potential (PLP) torsion energy. It is shown that the CSA search method can find lower energy binding poses than the Lamarckian genetic algorithm of AutoDock.

In silico study of the inhibition of DNA polymerase by a novel catalpol derivative

Osvaldo A. Martin, Hugo A. Garro, Marcela B. Kurina Sanz, Carlos Rodolfo Pungitore [Universidad Nacional de San Luis] and Carlos E. Tonn

J. Mol.Mod., **17**, 2717-2723, 2011.

In this work, a novel catalpol derivative (6,10,2',6'-tetraacetyl-O-catalpol), which was previously obtained by our group and shown experimentally to inhibit a type of Taq DNA polymerase, was studied in silico. Studies of the interaction of 6,10,2',6'-tetraacetyl-O-catalpol with the KlenTaq fragment of the Taq DNA polymerase I from *Thermus aquaticus* helped to elucidate the mechanism of inhibition of the enzyme, and offered valuable information that can be used to propose substrate structural modifications aimed at increasing the binding affinity.

Evaluation of Several Two-Step Scoring Functions Based on Linear Interaction Energy, Effective Ligand Size, and Empirical Pair Potentials for Prediction of Protein–Ligand Binding Geometry and Free Energy

Obaidur Rahaman, Trilce P. Estrada, Douglas J. Doren, Michela Taufer, Charles L. Brooks, III, and Roger S. Armen [Thomas Jefferson University]

J.Chem. Infor. and Mod. **51**, 2047–2065, 2011.

The performances of several two-step scoring approaches for molecular docking were assessed for their ability to predict binding geometries and free energies. Two new scoring functions designed for “step 2 discrimination” were proposed and compared to our CHARMM implementation of the linear interaction energy (LIE) approach using the Generalized-Born with Molecular Volume (GBMV) implicit solvation model. A scoring function S1 was proposed by considering only “interacting” ligand atoms as the “effective size” of the ligand and extended to an empirical regression-based pair potential S2.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 32(15), November, 2011.

- 3143–3153 **Modeling the interactions between polyoxometalates and their environment**, Blandine Courcot [The University of Sydney, Sydney] and Adam J. Bridgeman

To develop a force field suitable both for polyoxometalates (POMs) and organic cations, the Merck molecular force field 94x (MMFF94x) has been selected to describe the counterions used in POMs synthesis and has been combined with our force field optimized for type-II POMs with electrostatic and Van der Waals interactions included in the potential.

- 3154–3167 **Zinc–Homocysteine binding in cobalamin-dependent methionine synthase and its role in the substrate activation: DFT, ONIOM, and QM/MM molecular dynamics studies**, Safwat Abdel-Azeim, Xin Li, Lung Wa Chung and Keiji Morokuma [Kyoto University]

See Methodology / QM and QM/MM.

- 3168–3174 **The coupling constant polarizability and hyperpolarizability of $^1J(\text{NH})$ in N-methylacetamide, and its application for the multipole spin–spin coupling constant polarizability/reaction field approach to solvation**, Hanna Kjær [University of Copenhagen], Stephan P. A. Sauer and Jacob Kongsted

We present a benchmark study of a combined multipole spin–spin coupling constant (SSCC) polarizability/reaction field (MJP/RF) approach to the calculation of both specific and bulk solvation effects on SSCCs of solvated molecules.

- 3175–3187 **Accurate prediction of the enthalpies of formation for xanthophylls**, Jenn-Huei Lii, Fu-Xing Liao and Ching-Han Hu [National Changhua University of Education]

See Applications / Free Energy Calculations.

- 3188–3193 **Fast and accurate computation schemes for evaluating vibrational entropy of proteins**, Beisi Xu, Hujun Shen, Xiao Zhu and Guohui Li [The Chinese Academy of Sciences]

See Applications / Free Energy Calculations.

- 3194–3206 **In silico evaluation of proposed biosynthetic pathways for the unique dithiolate ligand of the H-cluster of [FeFe]-hydrogenase**, Alexios Grigoropoulos and Robert K. Szilagyi [Montana State University]

See Methodology / QM and QM/MM.

- 3207–3217 **New insights in quantum chemical topology studies using numerical grid-based analyses**, David Kozłowski and Julien Pilmé [Sorbonne Universités]

New insights in Quantum Chemical Topology of one-electron density functions have been proposed here by using a recent grid-based algorithm (Tang et al., J Phys Condens Matter 2009, 21, 084204), initially designed for the decomposition of the electron density.

3218–3225 Density functional theory study on electron and hole transport properties of organic pentacene derivatives with electron-withdrawing substituent, Shuo Chai, Shu-Hao Wen, Jin-Dou Huang and Ke-Li Han [Chinese Academy of Science]

Attaching electron-withdrawing substituent to organic conjugated molecules is considered as an effective method to produce n-type and ambipolar transport materials. In this work, we use density functional theory calculations to investigate the electron and hole transport properties of pentacene (PENT) derivatives after substituent and simulate the angular resolution anisotropic mobility for both electron and hole transport.

3226–3232 LigDockCSA: Protein–ligand docking using conformational space annealing, Woong-Hee Shin, Lim Heo, Juyong Lee, Junsu Ko, Chaok Seok [Seoul National University] and Jooyoung Lee

See Methodology / Ligand Docking.

3233–3240 Using Huffman coding method to visualize and analyze DNA sequences, Zhao-Hui Qi [Shijiazhuang Tiedao University], Ling Li and Xiao-Qin Qi

On the basis of the Huffman coding method, we propose a new graphical representation of DNA sequence. The representation can avoid degeneracy and loss of information in the transfer of data from a DNA sequence to its graphical representation.

3241–3252 QSPR study of Setschenow constants of organic compounds using MLR, ANN, and SVM analyses, Jie Xu [Wuhan Textile University], Lei Wang, Luoxin Wang, Xiaolin Shen and Weilin Xu

A quantitative structure-property relationship (QSPR) study was performed for the prediction of the Setschenow constants (K_{salt}) by sodium chloride of organic compounds.

3253–3263 Soft-core potentials in thermodynamic integration: Comparing one- and two-step transformations, Thomas Steinbrecher [Universität Karlsruhe], InSuk Joung and David A. Case

See Methodology / Solvation Energy.

3264–3268 Interactions between free radicals and a graphene fragment: Physical versus chemical bonding, charge transfer, and deformation, Fengting T. Wang [Jilin University], Lei Chen, Chuanjin J. Tian, Yan Meng, Zhigang G. Wang, Ruiqin Q. Zhang, Mingxing X. Jin, Ping Zhang and Dajun J. Ding

The adsorption of six free radicals (FRs) respectively on a graphene fragment was studied using a density functional tight-binding method with the inclusion of an empirical dispersion term in total energy.

3269–3275 A semiempirical long-range corrected exchange correlation functional including a short-range Gaussian attenuation (LCgau-B97), Jong-Won Song, Daoling Peng and Kimihiko Hirao [Advanced Science Institute, RIKEN 2-1]

We applied an improved long-range correction scheme including a short-range Gaussian attenuation (LCgau) to the Becke97 (B97) exchange correlation functional.

- 3276–3282 **A theoretical study of CO adsorption on gold by Hückel theory and density functional theory calculations**, Keju Sun [Industrial Science and Technology (AIST), 1-8-31, Midorigaoka], Masanori Kohyama, Shingo Tanaka and Seiji Takeda

It is crucial to understand the nature of CO adsorption on gold so as to elucidate the mechanism of low-temperature CO oxidation on nanogold catalysts. We performed theoretical analysis of CO adsorption on gold by using Hückel theory and density functional theory (DFT) calculations.

- 3283–3295 **A finite field method for calculating molecular polarizability tensors for arbitrary multipole rank**, Dennis M. Elking, Lalith Perera, Robert Duke, Thomas Darden and Lee G. Pedersen [University of North Carolina]

A finite field method for calculating spherical tensor molecular polarizability tensors $\alpha_{lm;l'm'} = \partial \Delta_{lm} / \partial \square_{l'm'}^*$ by numerical derivatives of induced molecular multipole Δ_{lm} with respect to gradients of electrostatic potential $\square_{l'm'}^*$ is described for arbitrary multipole ranks l and l' .

- 3296–3303 **Interplay between halogen bond and lithium bond in MCN-LiCN-XCCH (M = H, Li, and Na; X = Cl, Br, and I) complex: The enhancement of halogen bond by a lithium bond**, Qingzhong Li [Yantai University], Ran Li, Zhenbo Liu, Wenzuo Li and Jianbo Cheng

Quantum chemical calculations have been performed to study the complex of MCN-LiCN-XCCH (M = H, Li, and Na; X = Cl, Br, and I). The aim is to study the cooperative effect between halogen bond and lithium bond.

- 3304–3312 **An efficient parallel algorithm for the calculation of unrestricted canonical MP2 energies**, Jon Baker [Parallel Quantum Solutions] and Krzysztof Wolinski

We present details of our efficient implementation of full accuracy unrestricted open-shell second-order canonical Møller–Plesset (MP2) energies, both serial and parallel. The algorithm is based on our previous restricted closed-shell MP2 code using the Saebo–Almlöf direct integral transformation.

- 3313–3318 **Theoretical insights on the electron doping and Curie temperature in La-doped Sr_2CrWO_6** , Jing Wang, Jian Meng and Zhijian Wu [Changchun Institute of Applied Chemistry]

The structure and electronic and magnetic properties of $\text{La}_x\text{Sr}_{2-x}\text{CrWO}_6$ ($x = 0.0, 0.5, 1.0, 1.5, 2.0$) were investigated by using the density functional theory.

- 3319–3328 **Molecular dynamics simulations of triflic acid and triflate ion/water mixtures: A proton conducting electrolytic component in fuel cells**, Anurag Prakash Sunda and Arun Venkatnathan [Indian Institute of Science Education and Research]

Triflic acid is a functional group of perfluorosulfonated polymer electrolyte membranes where the sulfonate group is responsible for proton conduction. However, even at extremely low hydration, triflic acid exists as a triflate ion. In this work, we have developed a force-field for triflic acid and triflate ion by deriving force-field parameters using ab initio calculations and incorporated these parameters with the Optimized Potentials for Liquid Simulations - All Atom (OPLS-AA) force-field.

Journal of Molecular Modeling, 17(10), October, 2011.

- 2423-2442 **Can molecular dynamics simulations assist in design of specific inhibitors and imaging agents of amyloid aggregation? Structure, stability and free energy predictions for amyloid oligomers of VQIVYK, MVGGVV and LYQLEN**, Workalemahu Mikre Berhanu and Artëm E. Masunov [University of Central Florida]

See Applications / Protein Dynamics.

- 2443-2453 **Development of a QSPR model for predicting thermal stabilities of nitroaromatic compounds taking into account their decomposition mechanisms**, Guillaume Fayet[Parc Technologique Alata], Patricia Rotureau, Laurent Joubert and Carlo Adamo

The molecular structures of 77 nitroaromatic compounds have been correlated to their thermal stabilities by combining the quantitative structure–property relationship (QSPR) method with density functional theory (DFT).

- 2455-2464 **A molecular dynamics study on opioid activities of biphalin molecule**, Jin-Yuan Hsieh, Tzen-Yuh Chiang, Jun-Liang Chen, Chi-Chuan Hwang [National Cheng Kung University], Yun-Wen Chen and Hong-Chang Lin, et al.

See Applications / Ligand Binding.

- 2465-2473 **Prediction of zanamivir efficiency over the possible 2009 Influenza A (H1N1) mutants by multiple molecular dynamics simulations and free energy calculations**, Dabo Pan, Huijun Sun, Chongliang Bai, Huanxiang Liu [Lanzhou University], Yulin Shen and Nengzhi Jin, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 2475-2484 **Quantum chemical studies on the aminopolynitropyrazoles**, Pasupala Ravi [University of Hyderabad], Girish Mohan Gore, Surya Prakash Tewari and Arun Kanti Sikder

We have explored the geometric and electronic structures, band gap, thermodynamic properties, density, detonation velocity and detonation pressure of aminopolynitropyrazoles using the density functional theory (DFT) at the B3LYP/aug-cc-pVDZ level.

- 2485-2490 **The role of hydrogen bonds in an aqueous solution of acetylsalicylic acid: a molecular dynamics simulation study**, Maria Cristina Donnamaria [CICPBA] and Juan Roberto de Xammar Oro

See Applications / Medicinal Chemistry and Drug Design.

- 2491-2500 **The influence of secondary interactions on complex stability and double proton transfer reaction in 2-[1H]-pyridone/2-hydroxypyridine dimmers**, Borys Ośmiałowski [University of Technology and Life Sciences, Seminaryjna] and Robert Dobosz

The 2-[1H]-pyridone/2-hydroxypyridine tautomeric pair and its 6-substituted complexes have been studied with the use of DFT(M05) method.

- 2501-2511 **Topological description of the bond-breaking and bond-forming processes of the alkene protonation reaction in zeolite chemistry: an AIM study**, María Fernanda Zalazar and Nélide Maria Peruchena [Universidad Nacional del Nordeste]

Density functional theory and atoms in molecules theory were used to study bond breakage and bond formation in the trans-2-butene protonation reaction in an acidic zeolitic cluster.

- 2513-2523 **Insights into binding modes of 5-HT_{2c} receptor antagonists with ligand-based and receptor-based methods**, Chunhua Lu, Fangfang Jin, Cui Li, Weihua Li and Guixia Liu [East China University of Science and Technology], et al.

See Applications / Ligand Binding.

- 2525-2538 **Homology model and docking studies on porcine β_2 adrenoceptor: description of two binding sites**, Marvin A. Soriano-Ursúa [Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón], José Correa-Basurto, José G. Trujillo-Ferrara and Alberto J. Kaumann

See Applications / Homology Modeling.

- 2539-2547 **Light activation of the isomerization and deprotonation of the protonated Schiff base retinal**, Carlos Kubli-Garfias, Karim Salazar-Salinas, Emily C. Perez-Angel and Jorge M. Seminario [Texas A&M University]

We perform an ab initio analysis of the photoisomerization of the protonated Schiff base of retinal (PSB-retinal) from 11-cis to 11-trans rotating the C10-C11=C12-C13 dihedral angle from 0° (cis) to -180° (trans).

- 2549-2558 **Role of physicochemical properties in the activation of peroxisome proliferator-activated receptor δ** , Vinicius G. Maltarollo, Paula Homem-de-Mello and Káthia M. Honorio [Universidade Federal do ABC]

See Methodology / QM and QM/MM.

- 2559-2567 **In silico study on the substrate binding manner in human myo-inositol monophosphatase 2**, Seisuke Fujita, Tetsuo Ohnishi, Shujiro Okuda, Norihisa Fujita [Ritsumeikan University], Ryo Kobayashi and Satoshi Fukuno, et al.

See Applications / Homology Modeling.

- 2569-2574 **Sensitivity and the available free space per molecule in the unit cell**, Miroslav Pospíšil, Pavel Vávra, Monica C. Concha, Jane S. Murray and Peter Politzer [University of New Orleans]

Invoking the known link between impact sensitivity and compressibility, we have expanded upon an earlier preliminary study of the significance of the available free space per molecule in the unit cell, ΔV . We express ΔV as $V_{\text{eff}} - V_{\text{int}}$, where V_{eff} corresponds to zero free space, $V_{\text{eff}} = \frac{V}{\rho}$ molecular mass/density.

- 2575-2584 **Mechanistic study of the structure–activity relationship for the free radical scavenging activity of baicalein**, Zoran S. Marković, Jasmina M. Dimitrić Marković [University of Belgrade], Dejan Milenković and Nenad Filipović

See Methodology / QM and QM/MM.

- 2585-2600AM1 **parameters for palladium and silver**, Hakan Kayi and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg]

We report the parameterization of AM1* for the elements palladium and silver.

- 2601-2607 **SWIFT MODELLER: A JAVA based GUI for molecular modeling**, Abhinav Mathur, Shankaracharya and Ambarish S. Vidyarthi [Birla Institute of Technology, Mesra]

See Applications / Bioinformatics.

- 2609-2621 **Hydrogen bonding interactions in noradrenaline-DMSO complexes: DFT and QTAIM studies of structure, properties and topology**, Zhengguo Huang [Tianjin Normal University], Yumei Dai, Lei Yu and Hongke Wang

See Methodology / QM and QM/MM.

- 2623-2630 **DFT and MP2 investigations of L-proline and its hydrated complexes**, Xiao-Jun Li [Weinan Teachers University], Zhi-Jian Zhong and Hai-Zhen Wu

See Methodology / QM and QM/MM.

- 2631-2638 **Computational analysis of aspartic protease plasmepsin II complexed with EH58 inhibitor: a QM/MM MD study**, Natália de Farias Silva, Jerônimo Lameira and Cláudio Nahum Alves [Universidade Federal do Pará]

See Methodology / QM and QM/MM.

- 2639-2649 **The effect of a Pro28Thr point mutation on the local structure and stability of human galactokinase enzyme—a theoretical study**, Balázs Jójárt [University of Szeged], Milán Szőri, Róbert Izsák, István Marsi and Aranka László, et al.

See Applications / Protein Dynamics.

- 2651-2657 **Studies on filarial GST as a target for antifilarial drug development—in silico and in vitro inhibition of filarial GST by substituted 1,4-naphthoquinones**, Nisha Mathew [Indian Council of Medical Research], Lakshmy Srinivasan, Twinkle Karunan, Elango Ayyanar and Kalyanasundaram Muthuswamy

Eleven 1,4-naphthoquinone analogues with different amino substitutions at position 3 of the quinone ring earlier reported for macrofilaricidal activity were selected and screened against purified cytosolic GST isolated from the bovine filarial worm *Setaria digitata* and IC50 values were determined.

- 2659-2668 **Density functional theory study of the potassium complexation of an unsymmetrical 1,3-alternate calix[4]-crown-5-N-azacrown-5 bearing two different crown rings**, Xiaoyan Zheng, Xueye Wang [Xiangtan University], Keqi Shen, Yuan Miao and Dan Ouyang

Theoretical studies of an unsymmetrical calix[4]-crown-5-N-azacrown-5 (1) in a fixed 1,3-alternate conformation and the complexes 1•K+(a), 1•K+(b), 1•K+(c) and 1•K+K+ were performed using density functional theory (DFT) at the B3LYP/6-31G* level.

- 2669-2685 **Trajectory NG: portable, compressed, general molecular dynamics trajectories**, Daniel Spångberg [Uppsala University], Daniel S. D. Larsson and David van der Spoel

See Methodology / Molecular Dynamics.

- 2687-2692 **Computational study of proton and methyl cation affinities of imidazole-based highly energetic ionic liquids**, Hari Ji Singh [DDU Gorakhpur University] and Uttama Mukherjee

The present study deals with the evaluation of gas phase proton and methyl cation affinities for alkyl- and nitrosubstituted imidazoles using DFT (B3LYP)/6-31G(d) and MP2 methods in the Gaussian 03 software package.

- 2693-2705 **A comparative study of HIV-1 and HTLV-I protease structure and dynamics reveals a conserved residue interaction network**, Pia Rücker, Anselm H. C. Horn, Heike Meiselbach and Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

See Applications / Protein Dynamics.

- 2707-2716 **Ligand supported homology modeling and docking evaluation of CCR2: docked pose selection by consensus scoring**, Jong-Hoon Kim [Yonsei University], Jee Woong Lim, Seung-Woo Lee, Kyoungrak Kim and Kyoung Tai No

See Methodology / Homology Modeling.

- 2717-2723 **In silico study of the inhibition of DNA polymerase by a novel catalpol derivative**, Osvaldo A. Martin, Hugo A. Garro, Marcela B. Kurina Sanz, Carlos Rodolfo Pungitore [Universidad Nacional de San Luis] and Carlos E. Tonn

See Methodology / Ligand Binding.

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