



Results

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About 85 Papers from more than 30 Journals are cited.

1	APPLICATIONS (56)	Page 2		
1.1	Small Molecules (8)			
	Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 4
	QSAR	Page 4		
1.2	Biopolymers (46)			
	Bioinformatics and Cheminformatics	Page 5	Ligand Binding	Page 11
	Protein Structure Prediction	Page 6	Enzyme Catalysis	Page 12
	Comparative or Homology Modeling	Page 6	Protein-Protein Interactions	Page 13
	Protein Conformational Analysis	Page 7	Membrane Proteins	Page 14
	Protein Structure Analysis	Page 7	Protein Folding	Page 16
	Protein Dynamics	Page 8	Nucleic Acids	Page 17
	Free Energy Calculations	Page 10		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 17		
2	METHODOLOGY (13)	Page 18		
	QSAR	Page 18	QM & QM/MM	Page 20
	Potentials and Parameters	Page 18	Ligand Docking	Page 21
	Molecular Dynamics	Page 19		
3	JOURNAL REVIEWS (6)	Page 21		
	Journal of Molecular Graphics and Modeling, 72, March, 2017.			
	Journal of Computational Chemistry, 38 (2, 3), January, 2017.			
	Journal of Molecular Modeling, 23 (1), January, 2017.			
	Molecular Simulation, 43 (1, 2), January, 2017.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 30		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Design, synthesis, docking and QSAR study of substituted benzimidazole linked oxadiazole as cytotoxic agents, EGFR and erbB2 receptor inhibitors

Md Jawaid Akhtar, Anees Ahmad Siddiqui, Ahsan Ahmed Khan, Zulphikar Ali, Rikeshwer Prasad Dewangan, Santosh Pasha, M. Shahar Yar [Hamdard University]

Eur Jou Med Chem., **126**, 853-869, 2016.

The synthesis of benzimidazole linked oxadiazole derivatives designed as potential EGFR and erbB2 receptor inhibitors with anticancer and apoptotic activity were studied. Compounds 7a specifically inhibit EGFR and erbB2 receptor at 0.081 and 0.098 μM concentration. Some of the compounds showed strong, broad-spectrum antiproliferative activity when tested against five human cancer cell lines. Compounds 7a and 7n were more cytotoxic than 5-fluorouracil against MCF-7 cancer cell, with IC50 values of 5.0 and 2.55 μM whereas, only 7a led to cell cycle arrest at G2/M phase accompanied by an increase in apoptosis.

Synthesis, biological evaluation and in silico molecular modeling of pyrrolyl benzohydrazide derivatives as enoyl ACP reductase inhibitors

Shrinivas D. Joshi [S.E.T's College of Pharmacy], Sheshagiri R. Dixit, Venkatarao H. Kulkarni, Christian Lherbet, Mallikarjuna N. Nadagouda, Tejraj M. Aminabhavi

Eur Jou Med Chem., **126**, 286-297, 2016.

In efforts to develop lead anti-TB compounds, a novel series of 19 pyrrolyl benzohydrazides were synthesized and screened to target enoyl-ACP reductase enzyme, which is one of the important enzymes involved in type II fatty acid biosynthetic pathway of *M. tuberculosis*. Pharmacophores were constructed using GALAHAD to generate alignment of data sets and calculated by Pareto ranking. The pharmacophore features were then filtered by Surflex-dock study using enoyl ACP reductase from *M. tuberculosis*.



MMCC Results

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Medicinal Chemistry and Drug Design (Cont'd)

Development of CXCR4 modulators by virtual HTS of a novel amide-sulfamide compound library

Renren Bai, Qi Shi, Zhongxing Liang, Younghyun Yoon, Yiran Han, Amber Feng, Shuangping Liu, Yoonhyeun Oum, C. Chris Yun, Hyunsuk Shim [School of Medicine, Emory University]

Eur Jou Med Chem., **126**, 464-475, 2016.

CXCR4 plays a crucial role in recruitment of inflammatory cells to inflammation sites at the beginning of the disease process. Modulating CXCR4 functions presents a new avenue for anti-inflammatory strategies. However, using CXCR4 antagonists for a long term usage presents potential serious side effect due to their stem cell mobilizing property. We have been developing partial CXCR4 antagonists without such property. A new computer-aided drug design program, the FRESH workflow, was used for anti-CXCR4 lead compound discovery and optimization, which coupled both compound library building and CXCR4 docking screens in one campaign.

Unbinding pathway energy of glyphosate from the EPSPs enzyme binding site characterized by Steered Molecular Dynamics and Potential of Mean Force

Moacir F. Ferreira Júnior [Universidade Federal de Uberlândia], Eduardo F. Franca, Fábio L. Leite

J. Mol.Graph. and Mod., **72**, 43-49, 2017.

The quantification of herbicides in the environment, like glyphosate, is extremely important to prevent contamination. Nanobiosensors stands out in the quantization process, because of the high selectivity, sensitivity and short response time of the method. In order to emulate the detection of glyphosate using a specific nanobiosensor through an Atomic Force Microscope (AFM), this work carried out Steered Molecular Dynamics simulations (SMD) in which the herbicide was unbinded from the active site of the enzyme 5-enolpyruvylshikimate 3 phosphate synthase (EPSPS) along three different directions.

Towards the understanding of tetrahydroquinolines action in *Aedes aegypti*: larvicide or adulticide?

Juliana de O. S. Giacoppo, Juliano B. Carregal, Moacyr C. Junior, Elaine F. F. da Cunha & Teodorico C. Ramalho [Federal University of Lavras]

Molec. Simul., **43**, 121-133, 2017.

Aedes aegypti is an important vector of arboviruses such as dengue, yellow fever, chikungunya and Zika. Among the various types of insecticides used to combat this vector, the insect growth regulators have been developed and recommended for control of their larvae. In this work compounds with proven regulatory action, tetrahydroquinolines will be studied. These regulators act on the hormones responsible for the insect development.

Quantitative Structure-Activity Relations

Informing the Human Plasma Protein Binding of Environmental Chemicals by Machine Learning in the Pharmaceutical Space: Applicability Domain and Limits of Predictability

Brandall L. Ingle, Brandon C. Veber, John W. Nichols and Rogelio Tornero-Velez [U.S. Environmental Protection Agency]

J.Chem. Infor. and Mod., **56**, 2243–2252, 2016.

The free fraction of a xenobiotic in plasma (Fub) is an important determinant of chemical adsorption, distribution, metabolism, elimination, and toxicity, yet experimental plasma protein binding data are scarce for environmentally relevant chemicals. The presented work explores the merit of utilizing available pharmaceutical data to predict Fub for environmentally relevant chemicals via machine learning techniques. Quantitative structure–activity relationship (QSAR) models were constructed with k nearest neighbors (kNN), support vector machines (SVM), and random forest (RF) machine learning algorithms from a training set of 1045 pharmaceuticals.

Debunking the Idea that Ligand Efficiency Indices Are Superior to pIC50 as QSAR Activities

Robert P. Sheridan [Modeling and Informatics Department, Merck & Co. Inc.]

J.Chem. Infor. and Mod., **56**, 2253–2262, 2016.

Several papers have appeared in which a ligand efficiency index instead of pIC50 is used as the activity in QSAR. The claim is that better fits and predictions are obtained with ligand efficiency. We show on both public-domain and in-house data sets that the apparent superiority is a statistical artifact that occurs when ligand efficiency indices are correlated with the physical property included in their definition (number of non-hydrogens, ALOGP, TPSA, etc.) and when the property is easier to predict than the original pIC50.

Carbon Nanoparticles

Effect of various surface conditions on nanochannel flows past permeable walls

Jian-Fei Xie & Bing-Yang Cao [Tsinghua University, Beijing]

Molec. Simul., **43**, 65-75, 2017.

In this paper, effects of surface conditions on the gas flow in nanochannels with permeable walls have been investigated by molecular dynamics simulations. The hydrodynamic characteristics of the gas flow in nanochannels, including the density distributions, slip length and boundary friction coefficient, have been significantly influenced by the molecular interactions between gas molecules and wall atoms. The density layering phenomena are observed at the fluid–wall interface under a strong fluid–wall interaction (FWI).

1.2. Biopolymers

Bioinformatics and Cheminformatics

Online interactive analysis of protein structure ensembles with Bio3D-web

Lars Skjærven, Shashank Jariwala, Xin-Qiu Yao, and Barry J. Grant [University of Michigan Medical School, Ann Arbor]

Bioinformatics. **32**, 3510-3512, 2016.

Bio3D-web is an online application for analyzing the sequence, structure and conformational heterogeneity of protein families. Major functionality is provided for identifying protein structure sets for analysis, their alignment and refined structure superposition, sequence and structure conservation analysis, mapping and clustering of conformations and the quantitative comparison of their predicted structural dynamics.

Integrating genomic information with protein sequence and 3D atomic level structure at the RCSB protein data bank

Andreas Prlić [San Diego Supercomputer Center, La Jolla], Tara Kalro, Roshni Bhattacharya, Cole

Bioinformatics. **32**, 3833-3835, 2016.

The Protein Data Bank (PDB) now contains more than 120,000 three-dimensional (3D) structures of biological macromolecules. To allow an interpretation of how PDB data relates to other publicly available annotations, we developed a novel data integration platform that maps 3D structural information across various datasets. This integration bridges from the human genome across protein sequence to 3D structure space. We developed novel software solutions for data management and visualization, while incorporating new libraries for web-based visualization using SVG graphics.

GPU-Accelerated Exploration of Biomolecular Energy Landscapes

Rosemary G. Mantell, Catherine E. Pitt, David J. Wales [Lensfield Road, Cambridge]

J. Chem. Theor. and Comp, **12**, 6182–6191, 2016.

We present graphics processing unit (GPU)-acceleration of various computational energy landscape methods for biomolecular systems. Basin-hopping global optimization, the doubly nudged elastic band method (DNEB), hybrid eigenvector-following (EF), and a local rigid body framework are described, including details of GPU implementations. We analyze the results for eight different system sizes, and consider the effects of history size for minimization and local rigidification on the overall efficiency.

Protein Structure Prediction

Use of Restraints from Consensus Fragments of Multiple Server Models To Enhance Protein-Structure Prediction Capability of the UNRES Force Field

Magdalena A. Mozolewska, Paweł Krupa, Bartłomiej Zaborowski, Adam Liwo [University of Gdańsk], Jooyoung Lee, Keehyoung Joo and Cezary Czaplewski

J.Chem. Infor. and Mod., **56**, 2263–2279, 2016.

Recently, we developed a new approach to protein-structure prediction, which combines template-based modeling with the physics-based coarse-grained UNited RESidue (UNRES) force field. In this approach, restrained multiplexed replica exchange molecular dynamics simulations with UNRES, with the α -distance and virtual-bond-dihedral-angle restraints derived from knowledge-based models are carried out. In this work, we report a test of this approach in the 11th Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction (CASP11), in which we used the template-based models from early-stage predictions by the LEE group CASP11 server (group 038, called “nns”), and further improvement of the method.

Structural Stability of Intellectin-1

John J. Kozak, Harry B. Gray and Roberto A. Garza-López [Pomona College, Claremont]

J. Phys. Chem. B., **120**, 11888–11896, 2016.

We study the structural stability of helical and nonhelical regions in chain A of human intelectin-1. Using a geometrical model introduced previously, we carried out a computational analysis based on the recently reported crystal structure of this protein by Kiessling et al. to quantify the resiliency of the native state to steric perturbations. Response to these perturbations is characterized by calculating, relative to the native state, the lateral, radial, and angular displacements of n-residue segments of the polypeptide chain centered on each residue.

Comparative or Homology Modeling

PPI4DOCK: large scale assessment of the use of homology models in free docking over more than 1000 realistic targets

Jinchao Yu and Raphaël Guerois [Université Paris-Saclay]

Bioinformatics. **32**, 3760-3767, 2016.

Protein–protein docking methods are of great importance for understanding interactomes at the structural level. It has become increasingly appealing to use not only experimental structures but also homology models of unbound subunits as input for docking simulations. We explored how we could benefit from comparative modelling of unbound subunits to expand docking benchmark datasets. Starting from a collection of 3157 non-redundant, high X-ray resolution heterodimers, we developed the PPI4DOCK benchmark containing 1417 docking targets based on unbound homology models.

Protein Confirmation Analysis

Conformational Heterogeneity of Intracellular Loop 3 of the μ -opioid G-protein Coupled Receptor

Jing Huang, Sirish Kaushik Lakkaraju, Andrew Coop and Alexander D. MacKerell Jr. [University of Maryland, Baltimore]

J. Phys. Chem. B., **120**, 11897–11904, 2016.

G-protein coupled receptors (GPCRs), including the μ -opioid receptor, interact with G-proteins and other proteins via their intracellular face as required for signal transduction. However, characterization of the structure of the intracellular face of GPCRs is complicated by the experimental methods used for structural characterization. In the present study we undertook a series of long-time molecular dynamics (MD) simulations, ranging from 1 to 5 μ s, on the μ -opioid receptor in both the dimeric and monomeric states.

Capturing the Membrane-Triggered Conformational Transition of an α -Helical Pore-Forming Toxin

V. V. Hemanth Giri Rao, Rajat Desikan, K. Ganapathy Ayappa and Shachi Gosavi [Tata Institute of Fundamental Research, Bengaluru]

J. Phys. Chem. B., **120**, 12064–12078, 2016.

Escherichia coli cytolysin A (ClyA) is an α -helical pore-forming toxin (PFT) which lyses target cells by forming membrane permeabilizing pores. The rate-determining step of this process is the conversion of the soluble ClyA monomer into a membrane inserted protomer. We elucidate the mechanism of this conformational transition using molecular dynamics simulations of coarse-grained models of ClyA and a membrane.

Protein Structure Analysis

Probing the Structure of the Escherichia coli Periplasmic Proteins HdeA and YmgD by Molecular Dynamics Simulations

Eileen Socher and Heinrich Sticht [Friedrich-Alexander-University Erlangen-Nürnberg]

J. Phys. Chem. B., **120**, 11845–11855, 2016.

HdeA and YmgD are structurally homologous proteins in the periplasm of Escherichia coli. HdeA has been shown to represent an acid-activated chaperone, whereas the function of YmgD has not yet been characterized. We performed pH-titrating molecular dynamics simulations (pHtMD) to investigate the structural changes of both proteins and to assess whether YmgD may also exhibit an unfolding behavior similar to that of HdeA. The unfolding pathway of HdeA includes partially unfolded dimer structures, which represent a prerequisite for subsequent dissociation.

Mechanism of Nucleation and Growth of A β 40 Fibrils from All-Atom and Coarse-Grained Simulations

Sukanya Sasmal, Nadine Schwierz and Teresa Head-Gordon [University of California, Berkeley]

J. Phys. Chem. B., **120**, 12088–12097, 2016.

In this work, we characterize the nucleation and elongation mechanisms of the “diseased” polymorph of the amyloid- β 40 (A β 40) fibril using an off-lattice coarse-grained (CG) protein model. After determining the nucleation size and subsequent stable protofibrillar structure from the CG model, validated with all-atom simulations, we consider the “lock and dock” and “activated monomer” fibril elongation mechanisms for the protofibril by statistical additions of a monomer drawn from four different ensembles of the free A β 40 peptide to grow the fibril.

Protein Dynamics

The Dynamic Behavior of the P2X4 Ion Channel in the Closed Conformation

Gustavo Pierdominici-Sottile [Universidad Nacional de Quilmes], Luciano Moffatt, Juliana Palma

Biophysical Journal., **111**, 2642-2650, 2016.

We present the results of a detailed molecular dynamics study of the closed form of the P2X4 receptor. The fluctuations observed in the simulations were compared with the changes that occur in the transition from the closed to the open structure. To get further insight on the opening mechanism, the actual displacements were decomposed into interchain motions and intrachain deformations. This analysis revealed that the iris-like expansion of the transmembrane helices mainly results from interchain motions that already take place in the closed conformation.

Exploring Protein Stability by Comparative Molecular Dynamics Simulations of Homologous Hyperthermophilic, Mesophilic, and Psychrophilic Proteins

Sara Khan, Umar Farooq [Carnegie Mellon University, Pittsburgh] and Maria Kurnikova

J.Chem. Infor. and Mod., **56**, 2129–2139, 2016.

In the present studies, we analyzed the influence of temperature on the stability and dynamics of the α subunit of tryptophan synthase (TRPS) from hyperthermophilic, mesophilic, and psychrophilic homologues at different temperatures by molecular dynamics simulations. Employing different indicators such as root-mean-square deviations, root-mean-square fluctuations, principal component analysis, and free energy landscapes, this study manifests the diverse behavior of these homologues with changes in temperature.

A Hybrid Monte Carlo Scheme for Multibackbone Protein Design

Karen Druart, Julien Bigot, Edouard Audit and Thomas Simonson [Ecole Polytechnique, Palaiseau]

J. Chem. Theor. and Comp., **12**, 6035–6048, 2016.

Multistate protein design explores side chain mutations, with the backbone allowed to sample a small, predetermined library of conformations. To achieve Boltzmann sampling of sequences and conformations, we use a hybrid Monte Carlo (MC) scheme: a trial hop between backbone models is followed by a short MC segment where side chain rotamers adjust to the new backbone, before applying a Metropolis-like acceptance test. The theoretical form and a practical approximation for the acceptance test are derived.

Probing Hydration Patterns in Class-A GPCRs via Biased MD: The A2A Receptor

Syeda Rehana Zia, Roberto Gaspari, Sergio Decherchi and Walter Rocchia [Italian Institute of Technology, Via Morego]

J. Chem. Theor. and Comp., **12**, 6049–6061, 2016.

Herein, we present a new computational approach for analyzing hydration patterns in biomolecular systems. This protocol aims to efficiently identify regions where structural waters may be located and, in the case of protein–ligand binding, where displacing one or more water molecules could be advantageous in terms of affinity and/or residence time. We validated our approach on the adenosine A2A receptor, a target of significant pharmaceutical relevance.

Protein Dynamics (Cont'd)

TMFF—A Two-Bead Multipole Force Field for Coarse-Grained Molecular Dynamics Simulation of Protein

Min LiFengjiao Liu and John Z. H. Zhang [East China Normal University]

J. Chem. Theor. and Comp., **12**, 6147–6156, 2016.

Coarse-grained (CG) models are desirable for studying large and complex biological systems. In this paper, we propose a new two-bead multipole force field (TMFF) in which electric multipoles up to the quadrupole are included in the CG force field. The inclusion of electric multipoles in the proposed CG force field enables a more realistic description of the anisotropic electrostatic interactions in the protein system and, thus, provides an improvement over the standard isotropic two-bead CG models. In order to test the accuracy of the new CG force field model, extensive molecular dynamics simulations were carried out for a series of benchmark protein systems.

Micelles of Gradient vs Diblock Copolymers: Difference in the Internal Structure and Properties

Vitaly S. Kravchenko and Igor I. Potemkin [Lomonosov Moscow State University]

J. Phys. Chem. B., **120**, 12211–12217, 2016.

We performed computer simulations to reveal a difference in internal structures of micelles formed by AB gradient copolymers and equivalent diblock copolymers in a selective solvent. In contrast to distinct core-shell structure of the diblock copolymer micelles (DCM), the soluble and insoluble monomer units are less segregated in the gradient copolymer micelles (GCM). Furthermore, the concentration of the soluble units in the GCM has a maximum at the core-corona interface.

Thermodynamics of Macromolecular Association in Heterogeneous Crowding Environments: Theoretical and Simulation Studies with a Simplified Model

Tadashi Ando, Isseki Yu, Michael Feig and Yuji Sugita [RIKEN Quantitative Biology Center (QBiC)]

J. Phys. Chem. B., **120**, 11856–11865, 2016.

The cytoplasm of a cell is crowded with many different kinds of macromolecules. The macromolecular crowding affects the thermodynamics and kinetics of biological reactions in a living cell, such as protein folding, association, and diffusion. We evaluate the free energy changes upon macromolecular association in a cell-like inhomogeneous crowding system via a theory of hard-sphere fluids and free energy calculations using Brownian dynamics trajectories.

Destabilization of Human Serum Albumin by Ionic Liquids Studied Using Enhanced Molecular Dynamics Simulations

Vance W. Jaeger and Jim Pfaendtner [University of Washington, 105 Benson Hall]

J. Phys. Chem. B., **120**, 12079–12087, 2016.

Ionic liquid (IL) containing solvents can change the structure, dynamics, function, and stability of proteins. In order to investigate the mechanisms by which ILs induce structural changes in a large multidomain protein, we study the interactions of human serum albumin (HSA) with two different ILs, 1-butyl-3-methylimidazolium tetrafluoroborate and choline dihydrogen phosphate. Root mean square deviation and fluctuation calculations indicate that high concentrations of ILs in mixtures with water lead to protein structures that remain close to their crystallographic structures on time scales of hundreds of nanoseconds.

Protein Dynamics (Cont'd)

Temperature-induced unfolding behavior of proteins studied by tensorial elastic network model

Amit Srivastava [University of Pittsburgh] and Rony Granek

Proteins: Stru. Fun. & Bioinf., **84**, 1767–1775, 2016.

Motivated by single molecule experiments and recent molecular dynamics (MD) studies, we propose a simple and computationally efficient method based on a tensorial elastic network model to investigate the unfolding pathways of proteins under temperature variation. The tensorial elastic network model, which relies on the native state topology of a protein, combines the anisotropic network model, the bond bending elasticity, and the backbone twist elasticity to successfully predicts both the isotropic and anisotropic fluctuations in a manner similar to the Gaussian network model and anisotropic network model.

Toward elucidating the heat activation mechanism of the TRPV1 channel gating by molecular dynamics simulation

Han Wen, Feng Qin and Wenjun Zheng [State University of New York at Buffalo]

Proteins: Stru. Fun. & Bioinf., **84**, 1938–1949, 2016.

As a key cellular sensor, the TRPV1 cation channel undergoes a gating transition from a closed state to an open state in response to various physical and chemical stimuli including noxious heat. Despite years of study, the heat activation mechanism of TRPV1 gating remains enigmatic at the molecular level. Toward elucidating the structural and energetic basis of TRPV1 gating, we have performed molecular dynamics (MD) simulations (with cumulative simulation time of 3 μ s), starting from the high-resolution closed and open structures of TRPV1 solved by cryo-electron microscopy.

Free Energy Calculations

Hierarchical Protein Free Energy Landscapes from Variationally Enhanced Sampling

Patrick Shaffer, Omar Valsson and Michele Parrinello [Department of Chemistry and Applied Biosciences, ETH Zurich]

J. Chem. Theor. and Comp., **12**, 5751–5757, 2016.

In recent work, we demonstrated that it is possible to obtain approximate representations of high-dimensional free energy surfaces with variationally enhanced sampling (Shaffer, P.; Valsson, O.; Parrinello, M. *Proc. Natl. Acad. Sci.*, 2016, 113, 17). The high-dimensional spaces considered in that work were the set of backbone dihedral angles of a small peptide, Chignolin, and the high-dimensional free energy surface was approximated as the sum of many two-dimensional terms plus an additional term which represents an initial estimate. In this paper, we build on that work and demonstrate that we can calculate high-dimensional free energy surfaces of very high accuracy by incorporating additional terms.

Ligand Binding/Docking

Discovery of Mycobacterium tuberculosis InhA Inhibitors by Binding Sites Comparison and Ligands Prediction

Tanja Štular, Samo Lešnik, Kaja Rožman, Julia Schink, Mitja Zdouc, An Ghysels, Feng Liu, Courtney C. Aldrich, V. Joachim Haupt, Sebastian Salentin, Simone Daminelli, Michael Schroeder, Thierry Langer, Stanislav Gobec, Dušanka Janežič, Janez Konc [National Institute of Chemistry, Hajdrihova]

Jou. Med. Chem., 59, 11069–11078, 2016.

Drug discovery is usually focused on a single protein target; in this process, existing compounds that bind to related proteins are often ignored. We describe ProBiS plugin, extension of our earlier ProBiS-ligands approach, which for a given protein structure allows prediction of its binding sites and, for each binding site, the ligands from similar binding sites in the Protein Data Bank. We developed a new database of precalculated binding site comparisons of about 290000 proteins to allow fast prediction of binding sites in existing proteins.

Chemotherapeutic drug selectivity between wild-type and mutant BRAF kinases in colon cancer

Jianchun Zhang, Tao Ji [Linyi People's Hospital]

J. Mol.Mod., 23, 1, 2017.

Oncogenic BRAF V600E mutation is involved in the development, invasion and metastasis of colon cancer. Selective inhibition of BRAFV600E mutant has been recognized as a therapeutic strategy for the cancer. Here, we carried out atomistic molecular dynamics (MD) simulations to characterize the structural basis, energetic property, and dynamics behavior of conformational change in BRAF activation loop upon the mutation. It is found that V600E mutation destabilizes inactive DFG-out conformation of activation loop and promotes its conversion to the active DFG-in conformation, thus conferring constitutive activity for BRAF kinase.

Identification of lead BAY60-7550 analogues as potential inhibitors that utilize the hydrophobic groove in PDE2A: a molecular dynamics simulation study

Jitendra Kumar, Tarana Umar, Tasneem Kausar, Mohammad Mobashir, Shahid M. Nayeem Nasimul Hoda [Jamia Millia Islamia, Central University]

J. Mol.Mod., 23, 7, 2017.

The phosphodiesterase (PDE) family of proteins are important regulators of signal transduction, which they achieve by controlling the secondary messengers cyclic AMP (cAMP) and cyclic GMP (cGMP). cAMP and cGMP are involved in many critical intracellular processes such as gene transcription, kinase activation, signal transduction in learning and memory, and channel function as secondary messengers. The involvement of PDEs in neuronal communication has made them important therapeutic targets.

Uncovering the Binding and Specificity of β -Wrapins for Amyloid- β and α -Synuclein

Asuka A. Orr, Michael M. Wördehoff, Wolfgang Hoyer, Phanourios Tamamis [Texas A&M University, College Station]

J. Phys. Chem. B., 120, 12781–12794, 2016.

Amyloidogenic proteins amyloid- β peptide (A β) and α -synuclein (α -syn) self-assemble into fibrillar amyloid deposits, senile plaques and Lewy bodies, pathological features of Alzheimer's and Parkinson's diseases, respectively. Interestingly, a portion of Alzheimer's disease cases also exhibit aggregation of α -syn into Lewy bodies, and growing evidence also suggests that A β and α -syn oligomers are toxic. , we used computational methods, primarily molecular dynamics simulations and free energy calculations, to shed light into the key interaction-based commonalities leading to the dual binding properties of β -wrapins.

Ligand Binding / Docking (Cont'd)

Compromise in competition between free energy and binding effect of intrinsically disordered protein p53 C-terminal domain

Mengzhi Han, Ji Xu & Ying Ren [Chinese Academy of Sciences, Beijing]

Molec. Simul., **43**, 110-120, 2017.

The C-terminal domain (CTD) of tumour suppressor p53 is an intrinsically disordered protein which has been shown to be able to bind multiple partner proteins and exercise diverse physiological functions in the cell. In this study, we performed molecular dynamics simulations on the isolated p53 CTD, as well as three regulatory binding complexes to investigate the conformational ensemble of isolated p53 CTD and its dynamic structures when different binding partner present.

Cofactors-loaded quaternary structure of lysine-specific demethylase 5C (KDM5C) protein: Computational model

Yunhui Peng and Emil Alexov [Clemson University, Clemson]

Proteins: Stru. Fun. & Bioinf., **84**, 1797–1809, 2016.

The KDM5C gene (also known as JARID1C and SMCX) is located on the X chromosome and encodes a ubiquitously expressed 1560-aa protein, which plays an important role in lysine methylation (specifically reverses tri- and di-methylation of Lys4 of histone H3). Currently, 13 missense mutations in KDM5C have been linked to X-linked mental retardation. In this work, we utilize homology modeling, docking, and experimental data to predict 3D structures of KDM5C domains and their mutual arrangement.

Determination of binding affinity upon mutation for type I dockerin-cohesin complexes from *Clostridium thermocellum* and *Clostridium cellulolyticum* using deep sequencing

Caitlin A. Kowalsky and Timothy A. Whitehead [Michigan State University, East Lansing]

Proteins: Stru. Fun. & Bioinf., **84**, 1914–1928, 2016.

The comprehensive sequence determinants of binding affinity for type I cohesin toward dockerin from *Clostridium thermocellum* and *Clostridium cellulolyticum* was evaluated using deep mutational scanning coupled to yeast surface display. We measured the relative binding affinity to dockerin for 2970 and 2778 single point mutants of *C. thermocellum* and *C. cellulolyticum*, respectively, representing over 96% of all possible single point mutants. The interface $\Delta\Delta G$ for each variant was reconstructed from sequencing counts and compared with the three independent experimental methods.

Enzyme Catalysis

Dynamic and Electrostatic Effects on the Reaction Catalyzed by HIV-1 Protease

Agnieszka Krzemińska, Vicent Moliner, Katarzyna Świderek [Lodz University of Technology]

J. Am. Chem. Soc., 138, 16283–16298, 2016.

HIV-1 Protease (HIV-1 PR) is one of the three enzymes essential for the replication process of HIV-1 virus, which explains why it has been the main target for design of drugs against acquired immunodeficiency syndrome (AIDS). This work is focused on exploring the proteolysis reaction catalyzed by HIV-1 PR, with special attention to the dynamic and electrostatic effects governing its catalytic power. Free energy surfaces for all possible mechanisms have been computed in terms of potentials of mean force (PMFs) within hybrid QM/MM potentials, with the QM subset of atoms described at semiempirical (AM1) and DFT (M06-2X) level.

Enzyme Catalysis (Cont'd)

Conformational Substrate Selection Contributes to the Enzymatic Catalytic Reaction Mechanism of Pin1

Esteban Vöhringer-Martinez [Universidad de Concepción],
Ciro Dörner

J. Phys. Chem. B., **120**, 12444–12453, 2016.

Conformational changes in enzymes and their role in their catalytic activity have been thoroughly addressed experimentally and theoretically. There is a vivid discussion in the field of enzyme catalysis on whether conformational changes of the enzyme are coupled to catalysis, or whether transition state stabilization through the preorganized protein and its electrostatic properties govern the catalysis. In this study, an additional contribution to the catalysis of one specific enzyme, Pin1, is proposed, which arises from its conformational selection of the peptide substrate from aqueous solution with the lowest activation barrier.

Molecular docking and molecular dynamics simulation approaches for identifying new lead compounds as potential AChE inhibitors

Jiancheng Shi, Wentong Tu, Min Luo & Chusheng Huang
[Guangxi Teachers Education University]

Molec. Simul., **43**, 102-109, 2017.

To provide hints for the design of novel acetylcholinesterase (AChE) inhibitors with higher potency and specificity, the binding modes of the (RS, S)-17b and (RS, R)-17b enantiomers on AChE were chosen to investigate by molecular docking and molecular dynamics simulation. The results show that the binding modes of (RS, S)-17b and (RS, R)-17b are clearly different from each other. In particular, the (RS, S)-17b and (RS, R)-17b enantiomers tend to be planar and bend conformations to interact with AChE, respectively.

Protein-Protein Interactions

PRODIGY: a web server for predicting the binding affinity of protein–protein complexes

Li C. Xue, João Pglm Rodrigues, Panagiotis L. Kastiris,
Alexandre Mjj Bonvin, and Anna Vangone [Utrecht
University]

Bioinformatics. **32**, 3676-3678, 2016.

Gaining insights into the structural determinants of protein–protein interactions holds the key for a deeper understanding of biological functions, diseases and development of therapeutics. An important aspect of this is the ability to accurately predict the binding strength for a given protein–protein complex. Here we present PROtein binDIng enerGY prediction (PRODIGY), a web server to predict the binding affinity of protein–protein complexes from their 3D structure.

Optimization and bioevaluation of Cdc37-derived peptides: An insight into Hsp90-Cdc37 protein-protein interaction modulators

Lei Wang, Li Li, Wei-Tao Fu, Zheng-Yu Jiang, Qi-Dong
You, Xiao-Li Xu [China Pharmaceutical University]

Bioorg. and Med. Chem., **24**, 233-240, 2016

Targeting Hsp90-Cdc37 protein-protein interaction (PPI) is becoming an alternative approach for future anti-cancer drug development. We previously reported the discovery of an eleven-residue peptide (Pep-1) with micromolar activity for the disruption of Hsp90-Cdc37 PPI. Efforts to improve upon the Pep-1 led to the discovery of more potent modulators for Hsp90-Cdc37 PPI. Through the analysis of peptides binding patterns, more peptides were designed for further verification which resulted in Pep-5, the shortest peptide targeting Hsp90-Cdc37, exerting the optimal structure and the most efficient binding mode.

Protein – Protein Interactions (Cont'd)

Discovery and Development of Kelch-like ECH-Associated Protein 1. Nuclear Factor Erythroid 2-Related Factor 2 (KEAP1:NRF2) Protein–Protein Interaction Inhibitors: Achievements, Challenges, and Future Directions

Zheng-Yu Jiang, Meng-Chen Lu and Qi-Dong You [China Pharmaceutical University, Nanjing]

Jou. Med. Chem., 59, 10837–10858, 2016.

The transcription factor Nrf2 is the primary regulator of the cellular defense system, and enhancing Nrf2 activity has potential usages in various diseases, especially chronic age-related and inflammatory diseases. Recently, directly targeting Keap1–Nrf2 protein–protein interaction (PPI) has been an emerging strategy to selectively and effectively activate Nrf2. This Perspective summarizes the progress in the discovery and development of Keap1–Nrf2 PPI inhibitors.

Membrane Proteins and Lipid Peptide Interactions

Improving scoring-docking-screening powers of protein–ligand scoring functions using random forest

Cheng Wang and Yingkai Zhang [New York University]

J. Comp. Chem., **38**, 169–177, 2016.

The development of new protein–ligand scoring functions using machine learning algorithms, such as random forest, has been of significant interest. By efficiently utilizing expanded feature sets and a large set of experimental data, random forest based scoring functions (RFbScore) can achieve better correlations to experimental protein–ligand binding data with known crystal structures. In this work, to improve scoring-docking-screening powers of protein–ligand docking functions simultaneously, we have introduced a Δ vinaRF parameterization and feature selection framework based on random forest.

Rational Design of Thermodynamic and Kinetic Binding Profiles by Optimizing Surface Water Networks Coating Protein-Bound Ligands

Stefan G. Krimmer, Jonathan Cramer, Michael Betz, Veronica Fridh, Robert Karlsson, Andreas Heine and Gerhard Klebe [University of Marburg]

Jou. Med. Chem., 59, 10530–10548, 2016.

A previously studied congeneric series of thermolysin inhibitors addressing the solvent-accessible S2' pocket with different hydrophobic substituents showed modulations of the surface water layers coating the protein-bound inhibitors. Increasing stabilization of water molecules resulted in an enthalpically more favorable binding signature, overall enhancing affinity. Based on this observation, we optimized the series by designing tailored P2' substituents to improve and further stabilize the surface water network. MD simulations were applied to predict the putative water pattern around the bound ligands.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Coarse-Grained Simulations of Membrane Insertion and Folding of Small Helical Proteins Using the CABS Model

Wojciech Pulawski, Michal Jamroz, Michal Kolinski, Andrzej Kolinski and Sebastian Kmiecik [University of Warsaw, Pasteura 1]

J.Chem. Infor. and Mod., **56**, 2207–2215, 2016.

The CABS coarse-grained model is a well-established tool for modeling globular proteins (predicting their structure, dynamics, and interactions). Here we introduce an extension of the CABS representation and force field (CABS-membrane) to the modeling of the effect of the biological membrane environment on the structure of membrane proteins. We validate the CABS-membrane model in folding simulations of 10 short helical membrane proteins not using any knowledge about their structure.

Domain Stability in Biomimetic Membranes Driven by Lipid Polyunsaturation

Xubo Lin, Joseph H. Lorent, Allison D. Skinkle, Kandice R. Levental, M. Neal Waxham, Alemayehu A. Gorfe and Ilya Levental [The University of Texas Health Science Center at Houston]

J. Phys. Chem. B., **120**, 11930–11941, 2016.

Biological membranes contain a broad variety of lipid species whose individual physicochemical properties and collective interactions ultimately determine membrane organization. A key aspect of the organization of cellular membranes is their lateral subdivision into domains of distinct structure and composition. We assess the role of lipid acyl chain unsaturation as a driving force for phase separation using coarse-grained molecular dynamics (CGMD) simulations validated by model membrane experiments.

Modeling Membrane Protein–Ligand Binding Interactions: The Human Purinergic Platelet Receptor

D'Artagnan Greene, Wesley M. Botello-Smith, Alec Follmer, Li Xiao, Eleftherios Lambros and Ray Luo [University of California, Irvine]

J. Phys. Chem. B., **120**, 12293–12304, 2016.

Membrane proteins, due to their roles as cell receptors and signaling mediators, make prime candidates for drug targets. The computational analysis of protein–ligand binding affinities has been widely employed as a tool in rational drug design efforts. Although efficient implicit solvent-based methods for modeling globular protein–ligand binding have been around for many years, the extension of such methods to membrane protein–ligand binding is still in its infancy. In this study, we extended the widely used Amber/MMPBSA method to model membrane protein–ligand systems, and we used it to analyze protein–ligand binding for the human purinergic platelet receptor (P2Y₁₂R), a prominent drug target in the inhibition of platelet aggregation for the prevention of myocardial infarction and stroke.

Molecular Dynamics Simulation of Skin Lipids: Effect of Ceramide Chain Lengths on Bilayer Properties

Rakesh Gupta, Balarama Sridhar Dwadasi and Beena Rai [Tata Research Development and Design Centre]

J. Phys. Chem. B., **120**, 12536–12546, 2016.

Stratum corneum (SC), the outer layer of skin, serves as a barrier for pathogens and maintains the trans-epidermal water loss. The lipid matrix of SC is the major diffusion-rate-limiting pathway as molecules will have to pass through it. Ceramides play a key role in structuring and maintaining the barrier function of the skin. In this study, atomistic molecular dynamics (MD) simulations were used to systematically investigate the effects of the chain length of ceramide (CER) tails on the properties of the bilayer at a skin temperature of 310 K.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Simulation study of interaction mechanism between peptide and asymmetric membrane

X. C. He, Z. G. Qu [Xi'an Jiaotong University] & F. Xu

Molec. Simul., **43**, 34-41, 2017.

Cell-penetrating peptides (CPPs) are widely used as drug carriers, owing to their superior ability to cross cell membrane both alone and with cargos, such as genes and other particles. Understanding the translocation mechanism of CPP is significant for many therapeutic purposes, including targeting drug and gene delivery. In this study, we performed a coarse-grained molecular dynamics simulation to investigate the interaction mechanism between polyarginine peptides and asymmetric membranes.

Detecting the native ligand orientation by interfacial rigidity: SiteInterlock

Sebastian Raschka, Joseph Bemister-Buffington and Leslie A. Kuhn [Michigan State University, East Lansing]

Proteins: Stru. Fun. & Bioinf., **84**, 1888–1901, 2016.

Understanding the physical attributes of protein-ligand interfaces, the source of most biological activity, is a fundamental problem in biophysics. Knowing the characteristic features of interfaces also enables the design of molecules with potent and selective interactions. We explore a new approach, testing the hypothesis that protein-ligand binding results in computationally detectable rigidification of the protein-ligand interface.

Protein Folding

A Maximum-Caliber Approach to Predicting Perturbed Folding Kinetics Due to Mutations

Hongbin Wan, Guangfeng Zhou and Vincent A. Voelz [Temple University, Philadelphia]

J. Chem. Theor. and Comp., **12**, 5768–5776, 2016.

We present a maximum-caliber method for inferring transition rates of a Markov state model (MSM) with perturbed equilibrium populations given estimates of state populations and rates for an unperturbed MSM. It is similar in spirit to previous approaches, but given the inclusion of prior information, it is more robust and simple to implement. We examine its performance in simple biased diffusion models of kinetics and then apply the method to predicting changes in folding rates for several highly nontrivial protein folding systems for which non-native interactions play a significant role.

Temperature-mediated switching of protectant-denaturant behavior of trimethylamine-N-oxide and consequences on protein stability from a replica exchange molecular dynamics simulation study

Gargi Borgohain & Sandip Paul [Indian Institute of Technology – Guwahati]

Molec. Simul., **43**, 52-64, 2017.

The detailed mechanism of protein folding–unfolding processes with the aid of osmolytes has been a leading topic of discussion over many decades. We have used replica-exchange molecular dynamics simulation to propose the molecular mechanism of interaction of a 20-residue mini-protein with urea and trimethylamine N-oxide (TMAO) that act as denaturing and protecting osmolyte, respectively, in binary osmolyte solutions. Urea is found to exert its action by interacting directly with the protein residues. Temperature tolerance of TMAO's action is particularly emphasised in this study.

Nucleic Acids

Coarse-Grained Simulations Complemented by Atomistic Molecular Dynamics Provide New Insights into Folding and Unfolding of Human Telomeric G-Quadruplexes

Petr Stadlbauer, Liuba Mazzanti, Tristan Cagnolini, David J. Wales, Philippe Derreumaux, Samuela Pasquali and Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp., **12**, 6077–6097, 2016.

G-quadruplexes are the most important noncanonical DNA architectures. Many quadruplex-forming sequences, including the human telomeric sequence d(GGGTTA)_n, have been investigated due to their implications in cancer and other diseases, and because of their potential in DNA-based nanotechnology. Based on atomistic simulations of diverse classes of intermediates in G-quadruplex folding, we have suggested that the folding is an extremely multipathway process combining a kinetic partitioning mechanism with conformational diffusion.

Combining Simulations and Solution Experiments as a Paradigm for RNA Force Field Refinement

Andrea Cesari, Alejandro Gil-Ley and Giovanni Bussi [Scuola Internazionale Superiore di Studi Avanzati]

J. Chem. Theor. and Comp., **12**, 6192–6200, 2016.

Recent computational efforts have shown that the current potential energy models used in molecular dynamics are not accurate enough to describe the conformational ensemble of RNA oligomers and suggest that molecular dynamics should be complemented with experimental data. We here propose a scheme based on the maximum entropy principle to combine simulations with bulk experiments. In the proposed scheme, the noise arising from both the measurements and the forward models used to back-calculate the experimental observables is explicitly taken into account.

Surfaces, Catalysts, and Materials Subjects

Molecular dynamics study of micelles properties according to their size

S. Lebecque, J.M. Crowet, M.N. Nasir, M. Deleu, L. Lins [University of Liège]

J. Mol. Graph. and Mod., **72**, 6-15, 2017.

Surfactants are molecules able to spontaneously self-assemble to form aggregates with well-defined properties, such as spherical micelles, planar bilayers, cylindrical micelles or vesicles. Micelles have notably several applications in many domains, such as drug delivery or membrane protein solubilization. In this work, we use the MD approach developed by Yoshii et al. and extend it to surfactants with different structures. We aim to systematically investigate different micellar properties as a function of the aggregates size by a molecular dynamics approach, to get an insight into the micellar organization and to collect some relevant descriptors about micelle formation.

Surfaces, Catalysts and Material Subjects (Cont'd)

A molecular dynamics investigation into the mechanisms of material removal and subsurface damage of nanoscale high speed laser-assisted machining

Houfu Dai & Genyu Chen [Hunan University, Changsha]

Molec. Simul., **43**, 42-51, 2017.

Molecular dynamics is employed to study the mechanism of material removal and subsurface damage of monocrystalline silicon when it is under a nanoscale high-speed laser-assisted grinding of a diamond tip. Laser-assisted machining (LAM) is that the workpiece is locally heated by an intense laser beam before material removal. The effects of laser moving speed, laser pulse intensity and laser spot radius are thoroughly investigated in terms of atomic trajectories, phase transformation, temperature distribution, grinding temperature, grinding force and friction coefficient.

2. METHODOLOGY

Quantitative Structure-Activity Relations

QSAR Model of Unbound Brain-to-Plasma Partition Coefficient, $K_{p,uu,brain}$: Incorporating P-glycoprotein Efflux as a Variable

Elena Dolgikh [Eli Lilly and Company, Indianapolis], Ian A. Watson, Prashant V. Desai, Geri A. Sawada, Stuart Morton, Timothy M. Jones and Thomas J. Raub

J.Chem. Infor. and Mod., **56**, 2225–2233, 2016.

We report development and prospective validation of a QSAR model of the unbound brain-to-plasma partition coefficient, $K_{p,uu,brain}$, based on the in-house data set of ~1000 compounds. We discuss effects of experimental variability, explore the applicability of both regression and classification approaches, and evaluate a novel, model-within-a-model approach of including P-glycoprotein efflux prediction as an additional variable.

Potentials and Parameters

Predicting Regioselectivity and Lability of Cytochrome P450 Metabolism Using Quantum Mechanical Simulations

Jonathan D. Tyzack, Peter A. Hunt and Matthew D. Segall [Optibrium Ltd.]

J.Chem. Infor. and Mod., **56**, 2180–2193, 2016.

We describe methods for predicting cytochrome P450 (CYP) metabolism incorporating both pathway-specific reactivity and isoform-specific accessibility considerations. Semiempirical quantum mechanical (QM) simulations, parametrized using experimental data and ab initio calculations, estimate the reactivity of each potential site of metabolism (SOM) in the context of the whole molecule. Ligand-based models, trained using high-quality regioselectivity data, correct for orientation and steric effects of the different CYP isoform binding pockets.

Potentials and Parameters (Cont'd)

Extension of the Slipids Force Field to Polyunsaturated Lipids

Inna Ermilova, Alexander P. Lyubartsev [Stockholm University]

J. Phys. Chem. B., **120**, 12826–12842, 2016.

The all-atomic force field Slipids (Stockholm Lipids) for lipid bilayers simulations has been extended to polyunsaturated lipids. Following the strategy adopted in the development of previous versions of the Slipids force field, the parametrization was essentially based on high-level ab initio calculations. Atomic charges and torsion angles related to polyunsaturated lipid tails were parametrized using structures of dienes molecules. The new parameters of the force field were validated in simulations of bilayers composed of seven polyunsaturated lipids.

Molecular Dynamics

Implicit Solvent Model for Million-Atom Atomistic Simulations: Insights into the Organization of 30-nm Chromatin Fiber

Saeed Izadi, Ramu Anandakrishnan and Alexey V. Onufriev [Virginia Polytechnic Institute and State University]

J. Chem. Theor. and Comp., **12**, 5946–5959, 2016.

Molecular dynamics (MD) simulations based on the implicit solvent generalized Born (GB) models can provide significant computational advantages over the traditional explicit solvent simulations. However, the standard GB becomes prohibitively expensive for all-atom simulations of large structures; the model scales poorly, $\sim n^2$, with the number of solute atoms. Here we combine our recently developed optimal point charge approximation (OPCA) with the hierarchical charge partitioning (HCP) approximation to present an $\sim n \log n$ multiscale, yet fully atomistic, GB model (GB-HCPO).

Computational Methods for Configurational Entropy Using Internal and Cartesian Coordinates

Simon Hikiri, Takashi Yoshidome and Mitsunori Ikeguchi [Yokohama City University]

J. Chem. Theor. and Comp., **12**, 5990–6000, 2016.

The configurational entropy of solute molecules is a crucially important quantity to study various biophysical processes. Consequently, it is necessary to establish an efficient quantitative computational method to calculate configurational entropy as accurately as possible. In the present paper, we investigate the quantitative performance of the quasi-harmonic and related computational methods, including widely used methods implemented in popular molecular dynamics (MD) software packages, compared with the Clausius method, which is capable of accurately computing the change of the configurational entropy upon temperature change.

Na⁺ Binding Is Ineffective in Forming a Primary Substrate Pocket of Thrombin

Ikuo Kurisaki and Masataka Nagaoka [Nagoya University, Furo-cho]

J. Phys. Chem. B., **120**, 11873–11879, 2016.

Thrombin is a serine protease involved in the blood coagulation reaction, and it shows maximum enzymatic activity in the presence of Na⁺. It has been supposed that Na⁺ binding promotes conversion from the inactive form, with a collapsed primary substrate pocket (S1 pocket), to the active form, with a properly formed S1 pocket. We employed all-atom molecular dynamics simulations for both active and inactive forms of thrombin in the presence and absence of Na⁺ binding and examined the effect of Na⁺ binding on S1-pocket formation.

Molecular Dynamics (Cont'd)

Energetic and Dynamic Analysis of Transport of Na⁺ and K⁺ through a Cyclic Peptide Nanotube in Water and in Lipid Bilayers

Yeonho Song, Ji Hye Lee, Hoon Hwang, George C. Schatz and Hyonseok Hwang [Kangwon National University, Chuncheon]

J. Phys. Chem. B., **120**, 11912–11922, 2016.

Potential of mean force (PMF) profiles and position-dependent diffusion coefficients of Na⁺ and K⁺ are calculated to elucidate the translocation of ions through a cyclic peptide nanotube, composed of 8 × cyclo[-(d-Leu-Trp)4-] rings, in water and in hydrated DMPC bilayers. The PMF profiles and PMF decomposition analysis for the monovalent cations show that favorable interactions of the cations with the CPN as well as the lipid bilayer and dehydration free energy penalties are two major competing factors which determine the free energy surface for ion transport through CPNs both in water and in lipid bilayers.

The role of electrostatics in TrxR electron transfer mechanism: A computational approach

Vitor H. Teixeira, Ana Sofia C. Capacho and Miguel Machuqueiro [Universidade de Lisboa, Lisboa]

Proteins: Stru. Fun. & Bioinf., **84**, 1836–1843, 2016.

Thioredoxin reductase (TrxR) is an important enzyme in the control of the intracellular reduced redox environment. It transfers electrons from NADPH to several molecules, including its natural partner, thioredoxin. Although there is a generally accepted model describing how the electrons are transferred along TrxR, which involves a flexible arm working as a “shuttle,” the molecular details of such mechanism are not completely understood. In this work, we use molecular dynamics simulations with Poisson–Boltzmann/Monte Carlo pKa calculations to investigate the role of electrostatics in the electron transfer mechanism.

QM and QM/MM

Different QM/MM Approaches To Elucidate Enzymatic Reactions: Case Study on ppGalNAcT2

Pavel Janoš, Tomáš Trnka, Stanislav Kozmon, Igor Tvaroška and Jaroslav Koča [Masaryk University]

J. Chem. Theor. and Comp., **12**, 6062–6076, 2016.

Hybrid QM/MM computational studies can provide invaluable insight into the mechanisms of enzymatic reactions that can be exploited for rational drug design. Various approaches are available for such studies. However, their strengths and weaknesses may not be immediately apparent. Using the retaining glycosyltransferase ppGalNAcT2 as a case study, we compare different methodologies used to obtain reaction paths and transition state information. Ab Initio MD using CPMD coupled with the String Method is used to derive the minimum free energy reaction path.

Hydrogen Abstraction of Camphor Catalyzed by Cytochrome P450cam: A QM/MM Study

Rui Lai and Hui Li [University of Nebraska-Lincoln]

J. Phys. Chem. B., **120**, 12312–12320, 2016.

A combined quantum mechanics and molecular mechanics (QM/MM, QM = UB3LYP-D3, MM = AMBER) method is used to study the hydrogen abstraction reaction in P450cam catalyzed hydroxylation of camphor in the quartet state. Compared to QM/MM calculations in the literature, this study uses larger basis sets for the most important atoms at the active site and QM/MM Hessian harmonic frequency calculations to determine the standard Gibbs free energy of activation and kinetic isotope effect.

QM and QM/MM (Cont'd)

Thermal Isomerization Mechanism in Dronpa and Its Mutants

Daryna Smyrnova, Kirill Zinovjev, Iñaki Tuñón, Arnout Ceulemans [Department of Chemistry, KU Leuven]

J. Phys. Chem. B., **120**, 12820–12825, 2016.

The photoswitching speed of the reversibly switchable fluorescent proteins (RSFPs) from the family of green fluorescent proteins (GFPs) changes upon mutation which is of direct importance for various high-resolution techniques. Dronpa is one of the most used RSFPs. Its point mutants rsFastLime (Dronpa V157G) and rsKame (Dronpa V157L) exhibit a striking difference in their photoswitching speed. Here the QM/MM on-the-fly string method is used in order to explore the details of the thermal isomerization mechanism.

Ligand Docking

Rational design of cyclic peptides to disrupt TGF- β /SMAD7 signaling in heterotopic ossification

Biao Zhong, Chi Zhang, Shang Guo, Changqing Zhang [Shanghai Jiao Tong University Affiliated Sixth People's Hospital]

J. Mol. Graph. and Mod., **72**, 25-31, 2017.

The human TGF- β /SMAD7 signaling has been recognized as an attractive target of heterotopic ossification (HO). Here, we report a successful rational design of cyclic peptides to disrupt the signaling pathway by targeting TGF- β -receptor complex. The intermolecular interaction between TGF- β and its cognate receptor is characterized in detail using molecular dynamics simulation, binding energetic analysis, and alanine scanning. With the computational analysis a binding loop of receptor protein is identified that plays an essential role in the peptide-mediated TGF- β -receptor interaction.

Three pairs of weak interactions precisely regulate the G-loop gate of Kir2.1 channel

Junwei Li, Shaoying Xiao, Xiaoxiao Xie, Hui Zhou, Chunli Pang, Shanshan Li, Hailin Zhang, Diomedes E. Logothetis, Yong Zhan and Hailong An [Hebei University of Technology, Tianjin]

Proteins: Stru. Fun. & Bioinf., **84**, 1929–1937, 2016.

Kir2.1 (also known as IRK1) plays key roles in regulation of resting membrane potential and cell excitability. To achieve its physiological roles, Kir2.1 performs a series of conformational transition, named as gating. However, the structural basis of gating is still obscure. Here, we combined site-directed mutation, two-electrode voltage clamp with molecular dynamics simulations and determined that H221 regulates the gating process of Kir2.1 by involving a weak interaction network.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 72, March, 2017.

- 1-5 **Optimized Tersoff empirical potential for germanene**, Sayyed Jalil Mahdizadeh [Ferdowsi University of Mashhad], Golnoosh Akhlagi

In the current work, the issue of re-parameterization of Tersoff empirical potential model was addressed for 2D nanomaterial 'germanene' to be applied in molecular dynamics simulation based studies. The well-known chi-square minimization procedure was used to optimize the original Tersoff potential parameters.

- 6-15 **Molecular dynamics study of micelles properties according to their size**, S. Lebecque, J.M. Crowet, M.N. Nasir, M. Deleu, L. Lins [University of Liège]

See Applications / Surfaces, Catalysts and Material Subjects.

- 16-24 **ISO-MANM: An imitation based optimization tool for multilayer microwave absorbers**, A. Cheraghi, R. Malekfar [Tarbiat Modares University], S. Moemen Bellah, M. Parishani

We investigate the performance of 109 types of composition with complex permittivity and permeability properties in the frequency range of 1–12 GHz.

- 25-31 **Rational design of cyclic peptides to disrupt TGF- β /SMAD7 signaling in heterotopic ossification**, Biao Zhong, Chi Zhang, Shang Guo, Changqing Zhang [Shanghai Jiao Tong University Affiliated Sixth People's Hospital]

See Methodology / Ligand Docking.

- 32-42 **CHARMM force field parameters for 2'-hydroxybiphenyl-2-sulfinate, 2-hydroxybiphenyl, and related analogs**, Yue Yu, Ishan A. Fursule, Landon C. Mills, Derek L. Englert, Brad J. Berron, Christina M. Payne [University of Kentucky]

2'-hydroxybiphenyl-2-sulfinate (HBPS) desulfinase (DszB) catalyzes the cleavage of the carbon-sulfur bond from HBPS in the final step of microbial 4S pathway desulfurization reactions. DszB. To understand the molecular-level contributions to substrate and inhibitor binding to DszB, we plan to perform molecular dynamic simulations bound to an array of naphthenic molecules and biphenyl analogues of HBPS.

- 43-49 **Unbinding pathway energy of glyphosate from the EPSPs enzyme binding site characterized by Steered Molecular Dynamics and Potential of Mean Force**, Moacir F. Ferreira Júnior [Universidade Federal de Uberlândia], Eduardo F. Franca, Fábio L. Leite

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 38 (2), January, 2017.

- 65–80 **Using polarizable POSSIM force field and fuzzy-border continuum solvent model to calculate pKa shifts of protein residues**, Ity Sharma and George A. Kaminski [Worcester Polytechnic Institute]

Our Fuzzy-Border (FB) continuum solvent model has been extended and modified to produce hydration parameters for small molecules using Polarizable Simulations Second-order Interaction Model (POSSIM) framework with an average error of 0.136 kcal/mol.

- 81–86 **Relativistic (SR-ZORA) quantum theory of atoms in molecules properties**, James S. M. Anderson, Juan I. Rodríguez [Escuela Superior de Física y Matemáticas], Paul W. Ayers and Andreas W. Götz

The Quantum Theory of Atoms in Molecules (QTAIM) is used to elucidate the effects of relativity on chemical systems. To do this, molecules are studied using density-functional theory at both the nonrelativistic level and using the scalar relativistic zeroth-order regular approximation.

- 87–92 **Benchmarking of density functionals for a soft but accurate prediction and assignment of ^1H and ^{13}C NMR chemical shifts in organic and biological molecules**, Enrico Benassi [Scuola Superiore Normale]

A number of programs and tools that simulate ^1H and ^{13}C nuclear magnetic resonance (NMR) chemical shifts using empirical approaches are available. These tools are user-friendly, but they provide a very rough (and sometimes misleading) estimation of the NMR properties, especially for complex systems. An alternative, efficient, semi-empirical approach has been proposed by Bally, Rablen, Tantillo, and coworkers. This idea consists of creating linear calibrations models, on the basis of the application of different combinations of functionals and basis sets.

- 93–100 **d-electron count, ion-pairing and diagonal twist angles in metallo-bis(dithiolene) complexes**, Charles C. Kirkpatrick [Saint Louis University], John N. Truong and Bruce A. Kowert

Electronic structure calculations for late transition metals coordinated by two dithiolene ligands are found to be consistent with existing structures and also predict the geometries of Ni(I) species for which no solid state structures have been reported. Of particular interest are the compounds $[\text{M}(\text{mnt})_2]^{n-}$ ($\text{M} = \text{Ni}, \text{Pd}$, and Pt with $n = 1, 2, 3$; $\text{M} = \text{Cu}$ with $n = 2$).

- 101–109 **Full rate constant matrix contraction method for obtaining branching ratio of unimolecular decomposition**, Yosuke Sumiya, Tetsuya Taketsugu and Satoshi Maeda [Hokkaido University]

The branching ratio of unimolecular decomposition can be evaluated by solving the rate equations. Recent advances in automated reaction path search methods have enabled efficient construction of the rate equations based on quantum chemical calculations. However, it is still difficult to solve the rate equations composed of hundreds or more elementary steps. In this article, we introduce an efficient approach to obtain the branching ratio from a given set of rate equations.

- 110–115 **Direct determination of discrete harmonic bath parameters from molecular dynamics simulations**, Peter L. Walters, Thomas C. Allen and Nancy Makri [University of Illinois, Urbana]

We present a direct procedure for determining the parameters of a discrete harmonic bath modeling the influence of a complex condensed phase environment on the system of interest. The procedure employs an efficient discretization of the spectral density into modes that correspond to equal fractions of the reorganization energy.

- 116–126 **The quest for best suited references for configuration interaction singles calculations of core excited states**, Christopher Ehlert and Tillmann Klamroth [Universität Potsdam]

Near edge X-ray absorption fine structure (NEXAFS) simulations based on the conventional configuration interaction singles (CIS) lead to excitation energies, which are systematically blue shifted. In this work, we systematically vary the underlying SCF approaches, that is, based on HF or density functional theory, to identify best suited reference orbitals using a series of small test molecules.

Journal of Computational Chemistry, 38 (3), January, 2017.

- 133–143 **Theoretical study of the atrazine pesticide interaction with pyrophyllite and Ca²⁺-montmorillonite clay surfaces**, Bastien Belzunces, Sophie Hoyau, Magali Benoit, Nathalie Tarrat and Fabienne Bessac [Université de Toulouse]

Atrazine, a pesticide belonging to the s-triazine family, is one of the most employed pesticides. Due to its negative impact on the environment, it has been forbidden within the European Union since 2004 but remains abundant in soils. For these reasons, its behavior in soils and water at the atomic scale is of great interest. In this article, we have investigated, using DFT, the adsorption of atrazine onto two different clay surfaces: a pyrophyllite clay and an Mg-substituted clay named montmorillonite, with Ca²⁺ compensating cations on its surface.

- 144–151 **From C58 to C62 and back: Stability, structural similarity, and ring current**, Li-Hua Gan, Rui Wu, Jian-Lei Tian, Joseph Clarke, Christopher Gibson and Patrick W. Fowler [Sheffield University]

An increasing number of observations show that non-classical isomers may play an important role in the formation of fullerenes and their exo- and endo-derivatives. A quantum-mechanical study of all classical isomers of C58, C60, and C62, and all non-classical isomers with at most one square or heptagonal face, was carried out.

- 152–160 **Adaptive partitioning by local density-peaks: An efficient density-based clustering algorithm for analyzing molecular dynamics trajectories**, Song Liu, Lizhe Zhu, Fu Kit Sheong, Wei Wang and Xuhui Huang [The Hong Kong University of Science and Technology]

We present an efficient density-based adaptive-resolution clustering method APLoD for analyzing large-scale molecular dynamics (MD) trajectories. APLoD performs the k-nearest-neighbors search to estimate the density of MD conformations in a local fashion, which can group MD conformations in the same high-density region into a cluster.

- 161–168 **Developing multisite empirical force field models for Pt(II) and cisplatin**, John P. Cvitkovic and George A. Kaminski [Worcester Polytechnic Institute]

We have developed empirical force field parameters for Pt(II) and cisplatin. Two force field frameworks were used—modified OPLS-AA and our second-order polarizable POSSIM. A seven-site model was used for the

Pt(II) ion. The goal was to create transferable parameter sets compatible with the force field models for proteins and general organic compounds.

- 169–177 **Improving scoring-docking-screening powers of protein–ligand scoring functions using random forest**, Cheng Wang and Yingkai Zhang [New York University]

See Applications / Membrane Proteins and Lipid-Peptide Interactions.

- 178–188 **Deformed transition-state theory: Deviation from Arrhenius behavior and application to bimolecular hydrogen transfer reaction rates in the tunneling regime**, Valter H. Carvalho-Silva, Vincenzo Aquilanti, Heibbe C. B. de Oliveira and Kleber C. Mundim [Universidade Estadual de Goiás]

A formulation is presented for the application of tools from quantum chemistry and transition-state theory to phenomenologically cover cases where reaction rates deviate from Arrhenius law at low temperatures. A parameter is introduced to describe the deviation for the systems from reaching the thermodynamic limit and is identified as the linearizing coefficient in the dependence of the inverse activation energy with inverse temperature.

Journal of Molecular Modeling, 23 (1), January, 2017.

- 1 **Chemotherapeutic drug selectivity between wild-type and mutant BRAF kinases in colon cancer**, Jianchun Zhang, Tao Ji [Linyi People's Hospital]

See Applications / Ligand Binding.

- 2 **Atomistic study of mono/multi-atomic vacancy defects on the mechanical characterization of boron-doped graphene sheets**, A. R. Setoodeh [Shiraz University of Technology], H. Badjian, H. Shirzadi Jahromi

Graphene is known for its exceptional mechanical and electrical properties when in the form of a hexagonal monolayer of carbon atoms. In this study, the mechanical properties of hexagonal boron-doped graphene (h-BdGr) sheets with a 2% concentration of boron atoms distributed randomly throughout the layer were investigated.

- 3 **Evaluating frontier orbital energy and HOMO/LUMO gap with descriptors from density functional reactivity theory**, Ying Huang, Chunying Rong, Ruiqin Zhang, Shubin Liu [University of North Carolina]

Wave function theory (WFT) and density functional theory (DFT)—the two most popular solutions to electronic structure problems of atoms and molecules—share the same origin, dealing with the same subject yet using distinct methodologies. One question that needs to be addressed when using these approaches to appreciate properties related to molecular structure and reactivity is if there is any link between the two. In this work, we present a piece of strong evidence addressing that very question.

- 4 **Comparative simulation study of chemical synthesis of functional DADNE material**, Min Hsien Liu [Chung Cheng Institute of Technology], Chuan Wen Liu

Amorphous molecular simulation to model the reaction species in the synthesis of chemically inert and energetic 1,1-diamino-2,2-dinitroethene (DADNE) explosive material was performed in this work.

- 5 **A theoretical study of the diastereoselective allylation of aldehydes with new chiral allylsilanes**, Vincent Tognetti [Université de Rouen], Samir Bouzbouz, Laurent Joubert

In this paper, we investigate the reaction mechanism for the synthesis of new functionalized chiral hydroxyamides theoretically, using a concerted density functional theory (DFT)—conceptual DFT—quantum theory of atoms-in-molecules (QTAIM) approach, which casts light on the main physicochemical properties responsible for the observed selectivity.

- 6 **SEI-forming electrolyte additives for lithium-ion batteries: development and benchmarking of computational approaches**, Piotr Jankowski [Warsaw University of Technology, Władysław Wieczorek, Patrik Johansson

SEI-forming additives play an important role in lithium-ion batteries, and the key to improving battery functionality is to determine if, how, and when these additives are reduced. Here, we tested a number of computational approaches and methods to determine the best way to predict and describe the properties of the additives.

- 7 **Identification of lead BAY60-7550 analogues as potential inhibitors that utilize the hydrophobic groove in PDE2A: a molecular dynamics simulation study**, Jitendra Kumar, Tarana Umar, Tasneem Kausar, Mohammad Mobashir, Shahid M. Nayeem Nasimul Hoda [Jamia Millia Islamia, Central University]

See Applications / Ligand Binding.

- 8 **Molecular dynamics study of nitrogen diffusion in nanocrystalline iron**, Naiyer Razmara [Azarbaijan Shahid Madani University], Roghayeh Mohammadzadeh

To obtain a deeper understanding of the production of advanced high-nitrogen steels, the diffusivity of nitrogen in bcc iron was investigated at the nanoscale by molecular dynamics (MD) simulation using the modified embedded-atom method (MEAM) interatomic potential.

- 9 **Simulation of NMR chemical shifts in heterocycles: a method evaluation**, Alexander Buß, Rainer Koch [Carl von Ossietzky Universität Oldenburg]

An alternative approach to evaluating the performance of computational methods for predicting chemical shifts is presented. The influence of the theoretical level and basis set on the accuracy in calculating both proton and carbon NMR spectra of a large number of heterocyclic molecules is assessed using a linear regression method, thus omitting the need for a reference (as a potential source of error).

- 10 **Insight into electrostatic initiation of nitramine explosives**, Bisheng Tan, Zhipeng Li, Xudong Guo, Jingming Li, Yong Han, Xinping Long [China Academy of Engineering Physics (CAEP)]

The electrostatic safety of explosives is of great importance. However, the mechanism for the transfer of energy from an electrostatic spark to the reactive center of an explosive material is not well understood. Thus, in this work, we attempted to clarify the mechanism associated with the static-electricity-initiated detonation of explosives using a model of the interaction that incorporated relevant parameters.

- 11 **Mechanisms for nickel(0)/N-heterocyclic carbene-catalyzed intramolecular alkene hydroacylation: insights from a DFT study**, Qingxi Meng [Shandong Agricultural University], Fen Wang

Density functional calculations have been applied to study and elucidate nickel(0)/N-heterocyclic carbene-catalyzed intramolecular alkene hydroacylation.

- 12 **Synthesis and theoretical studies on nitrogen-rich salts of bis[4-nitraminofurazanyl-3-azoxy]azofurazan (ADNAAF)**, Chunmei Zheng, Yuting Chu, Liwen Xu, Wu Lei, Fengyun Wang, Mingzhu Xia [Nanjing University of Science and Technology]

Multi-furazan compounds bis[4-nitramino- furazanyl-3-azoxy]azofurazan (ADNAAF) and its derivatives were first synthesized by our research group, and their structures were characterized by IR, ¹H-NMR, ¹³C-NMR spectrums, and element analysis. ADNAAF was synthesized by nitration reaction of bis[4-aminofurazanyl-3-azoxy]azofurazan (ADAAF), and then reacted with ammonium hydroxide, hydrazine hydrate, and guanidine nitrate to obtain three salts marked as salt 1, 2, and 3, respectively.

Molecular Simulation, 43 (1), 2017.

- 1-12 **Investigating the effects of wettability and gaseous nanobubbles on roughened wall–fluid interface using molecular dynamics simulation**, Tsu-Hsu Yen [R.O.C. Naval Academy, Kaohsiung]

This paper reports on the use of molecular dynamics (MD) simulation to investigate the coupling effects of wettability, surface roughness and interfacial nanobubbles (INBs) on wall–fluid interfaces.

- 13-18 **Creating realistic silica nanopores for molecular dynamics simulations**, Julian Geske [Technische Universität Darmstadt] & Michael Vogel

We present a detailed approach to create realistic silica pores for computer simulations especially molecular dynamics (MD) simulations. These pores are essential for all different kinds of simulations with liquids in silica confinements.

- 19-27 **Solvation free energies of nucleic acid bases in ionic liquids**, Khairulazhar Jumbri, Nuno M. Micaelo & Mohd Basyaruddin Abdul Rahman [University Putra Malaysia, Serdang]

The solvation free energies of five nucleic acid bases in [C_nbim]Br (where n = 2, 4, 6) ionic liquids (ILs) were computed using the Bennett acceptance ratio (BAR) method employing molecular dynamics simulations.

- 28-33 **MCl₂ (M=Hg, Cd, Zn, Mn) catalysed hydrochlorination of acetylene – a Density Functional Theory study**, Hui Qi, Qiang Li, Zhousheng Mo, Xiaotong Zhang & Lijuan Song [Liaoning Shihua University, Fushun]

A Density Functional Theory method has been employed in this research to conduct an in-depth study of the correlation between the conversion of acetylene to vinyl chloride catalysed by MCl₂ (M=Hg, Cd, Zn, Mn) and the electron affinity.

- 34-41 **Simulation study of interaction mechanism between peptide and asymmetric membrane**, X. C. He, Z. G. Qu [Xi'an Jiaotong University] & F. Xu

See Applications / Membrane Proteins and Lipid-Peptide Interactions.

- 42-51 **A molecular dynamics investigation into the mechanisms of material removal and subsurface damage of nanoscale high speed laser-assisted machining**, Houfu Dai & Genyu Chen [Hunan University, Changsha]

See Applications / Surfaces, Catalysts and Material Subjects.

- 52-64 **Temperature-mediated switching of protectant-denaturant behavior of trimethylamine-N-oxide and consequences on protein stability from a replica exchange molecular dynamics simulation study**, Gargi Borgohain & Sandip Paul [Indian Institute of Technology – Guwahati]

See Applications / Protein Folding.

- 65-75 **Effect of various surface conditions on nanochannel flows past permeable walls**, Jian-Fei Xie & Bing-Yang Cao [Tsinghua University, Beijing]

See Applications / Carbon Nanotubes.

Molecular Simulation, 43 (2), 2017.

- 76-85 **A new kinetic Monte Carlo scheme with Gibbs ensemble to determine vapour–liquid equilibria**, Shiliang Johnathan Tan, D. D. Do [University of Queensland, St. Lucia] & D. Nicholson

We present a new kinetic Monte Carlo scheme, as an alternative to the Gibbs ensemble Monte Carlo (GEMC) method, to determine vapour–liquid equilibria using a canonical ensemble in a system composed of two boxes.

- 86-91 **Band gap and electronic properties of molybdenum disulphide under strain engineering: density functional theory calculations**, Chuong V. Nguyen [Duy Tan University, Da Nang], Victor V. Ilyasov, Hieu V. Nguyen & Hieu N. Nguyen

In this paper, we study the effect of uniaxial and biaxial strain on the structural and electronic properties of MoS₂ monolayers by first-principle calculations based on density functional theory.

- 92-101 **A coarse-grained model for PCL: conformation, self-assembly of MePEG-b-PCL amphiphilic diblock copolymers**, Abhinav S. Raman, Aleksey Vishnyakov & Y. C. Chiew [Rutgers University, Piscataway]

Poly-ε-caprolactone (PCL) is a biodegradable hydrophobic polyester that has been widely used in medical devices, tissue engineering and nanoparticle-based drug delivery. Coarse-grained molecular dynamics (CGMD) has been employed to study and gain insights into the conformational, structural and self-assembly behaviour of polymers, lipids and amphiphilic macromolecules. In this work, we developed a model for PCL within the framework of the MARTINI coarse-grained force field.

- 102-109 **Molecular docking and molecular dynamics simulation approaches for identifying new lead compounds as potential AChE inhibitors**, Jiancheng Shi, Wentong Tu, Min Luo & Chusheng Huang [Guangxi Teachers Education University]

See Applications / Enzyme Catalysis.

- 110-120 **Compromise in competition between free energy and binding effect of intrinsically disordered protein p53 C-terminal domain**, Mengzhi Han, Ji Xu & Ying Ren [Chinese Academy of Sciences, Beijing]

See Applications / Ligand Binding.

- 121-133 **Towards the understanding of tetrahydroquinolines action in *Aedes aegypti*: larvicide or adulticide?**, Juliana de O. S. Giacoppo, Juliano B. Carregal, Moacyr C. Junior, Elaine F. F. da Cunha & Teodorico C. Ramalho [Federal University of Lavras]

See Applications / Medicinal Chemistry and Drug Design.

- 134-140 **Potentials of mean force in acidic proton transfer reactions in constrained geometries**, Jordi Martí [Technical University of Catalonia-Barcelona Tech]

Free energy barriers associated with the transfer of an excess proton in water and related to the potentials of mean force in proton transfer episodes have been computed in a wide range of thermodynamic states, from low-density amorphous ices to high-temperature liquids under the critical point for unconstrained and constrained systems.

- 141-153 **DFT study on gas-phase hydrodeoxygenation of guaiacol by various reaction schemes**, Anand Mohan Verma & Nanda Kishore [Indian Institute of Technology, Guwahati]

Guaiacol is an important phenolic component present in pyrolytic bio-oils; and in this work its hydrodeoxygenation (HDO) by various reaction schemes has been considered within the framework of density functional theory. In this computational study, primarily three reaction schemes for the HDO of guaiacol are considered.

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About 110 Papers from more than 30 Journals are cited.

1 APPLICATIONS (83) Page 2

1.1 Small Molecules (15)

Water and Solvation	Page 2	QSAR	Page 6
Organic Solvents	Page 3	Host-Guest Systems	Page 6
Med. Chem. And Drug Design	Page 3		

1.2 Biopolymers (68)

Bioinformatics and Cheminformatics	Page 6	Enzyme Catalysis	Page 15
Protein Sequence Analysis	Page 8	Protein-Protein Interactions	Page 18
Protein Conformational Analysis	Page 8	Membrane Proteins	Page 19
Protein Structure Analysis	Page 10	Protein Folding	Page 21
Protein Dynamics	Page 11	Protein-Nucleic Acids	Page 23
Free Energy Calculations	Page 13	Nucleic Acids	Page 24
Ligand Binding	Page 13		

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (17) Page 26

Potentials and Parameters	Page 26	Comparative or Homology	Page 29
Molecular Dynamics	Page 27	Ligand Docking	Page 29
QM & QM/MM	Page 28		

3 JOURNAL REVIEWS (5) Page 31

Journal of Molecular Graphics and Modeling, 63, January, 2016.
 Journal of Computational Chemistry, 37 (3), January, 2016.
 Journal of Computational Chemistry, 37 (4, 5), February, 2016.
 Journal of Molecular Modeling, 22 (2), January, 2016.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 38

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Spatial Decomposition of Translational Water–Water Correlation Entropy in Binding Pockets

Crystal N. Nguyen, Tom Kurtzman, and Michael K. Gilson
[University of California San Diego]

J. Chem. Theor. and Comp, **12**, 414–429, 2016.

A number of computational tools available today compute the thermodynamic properties of water at surfaces and in binding pockets by using inhomogeneous solvation theory (IST) to analyze explicit-solvent simulations. Here, we present an extension of the Grid Inhomogeneous Solvation Theory (GIST) approach which accounts for water–water translational correlations.

Coarse-Grained Model for Water Involving a Virtual Site

Mingsen Deng and Hujun Shen [Guizhou Education University]

J. Phys. Chem. B., **120**, 733–739, 2016.

In this work, we propose a new coarse-grained (CG) model for water by combining the features of two popular CG water models (BMW and MARTINI models) as well as by adopting a topology similar to that of the TIP4P water model. In this CG model, a CG unit, representing four real water molecules, consists of a virtual site, two positively charged particles, and a van der Waals (vdW) interaction center. Distance constraint is applied to the bonds formed between the vdW interaction center and the positively charged particles.



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Organic Solvents

Predicting Partition Coefficients with a Simple All-Atom/Coarse-Grained Hybrid Model

Samuel Genheden [University of Gothenburg]

J. Chem. Theor. and Comp., **12**, 297–304, 2016.

The solvation free energy is an essential quantity in force field development and in numerous applications. Here, we present the estimation of solvation free energies in polar (water, hexanol, octanol, and nonanol) and in apolar (hexane, octane, and nonane) media. The estimates are produced using molecular dynamics simulations employing a simple all-atom/coarse-grained hybrid model (AA/ELBA) and are therefore very efficient. More than 150 solutes were taken from the Minnesota solvation database and represent small, organic molecules.

Medicinal Chemistry and Drug Design

Drug-set enrichment analysis: a novel tool to investigate drug mode of action

Francesco Napolitano, Francesco Sirci, Diego Carrella, and Diego di Bernardo [Telethon Institute of Genetics and Medicine]

Bioinformatics. **32**, 235-241, 2016.

Automated screening approaches are able to rapidly identify a set of small molecules inducing a desired phenotype from large small-molecule libraries. However, the resulting set of candidate molecules is usually very diverse pharmacologically, thus little insight on the shared mechanism of action (MoA) underlying their efficacy can be gained. We introduce a computational method (Drug-Set Enrichment Analysis—DSEA) based on drug-induced gene expression profiles, which is able to identify the molecular pathways that are targeted by most of the drugs in the set. By diluting drug-specific effects unrelated to the phenotype of interest, DSEA is able to highlight phenotype-specific pathways, thus helping to formulate hypotheses on the MoA shared by the drugs in the set.

Pharmacoinformatics analysis to identify inhibitors of Mtb-ASADH

Rajender Kumar, Prabha Garg [National Institute of Pharmaceutical Education and Research (NIPER)] & P.V. Bharatam

J. Biomol. Stru. and Dyn., **34**, 1-14, 2016.

Aspartate-semialdehyde dehydrogenase (ASADH; EC 1.2.1.11) is a key enzyme in the biosynthesis of essential amino acids in prokaryotes and fungi, inhibition of ASADH leads to the development of novel antitubercular agents. In the present work, a combined structure and ligand-based pharmacophore modeling, molecular docking, and molecular dynamics (MD) approaches were employed to identify potent inhibitors of mycobacterium tuberculosis (Mtb)-ASADH. The structure-based pharmacophore hypothesis consists of three hydrogen bond acceptor (HBA), two negatively ionizable, and one positively ionizable center, while ligand-based pharmacophore consists of additional one HBA and one hydrogen bond donor features.

Medicinal Chemistry and Drug Design (Cont'd)

Insights into molecular interactions between CaM and its inhibitors from molecular dynamics simulations and experimental data

Martin González-Andrade [Universidad Nacional Autónoma de México (UNAM)], Rogelio Rodríguez-Sotres, Abraham Madariaga-Mazón, José Rivera-Chávez, Rachel Mata, Alejandro Sosa-Peinado, Luis del Pozo-Yauner & Imilla I. Arias-Olguín

J. Biomol. Stru. and Dyn., **34**, 78-91, 2016.

In order to contribute to the structural basis for rational design of calmodulin (CaM) inhibitors, we analyzed the interaction of CaM with 14 classic antagonists and two compounds that do not affect CaM, using docking and molecular dynamics (MD) simulations, and the data were compared to available experimental data. The Ca²⁺-CaM-Ligands complexes were simulated 20 ns, with CaM starting in the “open” and “closed” conformations. The analysis of the MD simulations provided insight into the conformational changes undergone by CaM during its interaction with these ligands.

Multi-drug resistance profile of PR20 HIV-1 protease is attributed to distorted conformational and drug binding landscape: molecular dynamics insights

Sarentha Chetty, Soumendranath Bhakat, Alberto J.M. Martin & Mahmoud E.S. Soliman [University of Kwazulu-Natal]

J. Biomol. Stru. and Dyn., **34**, 135-151, 2016.

The PR20 HIV-1 protease, a variant with 20 mutations, exhibits high levels of multi-drug resistance; however, to date, there has been no report detailing the impact of these 20 mutations on the conformational and drug binding landscape at a molecular level. In this report, we demonstrate the first account of a comprehensive study designed to elaborate on the impact of these mutations on the dynamic features as well as drug binding and resistance profile, using extensive molecular dynamics analyses. Comparative MD simulations for the wild-type and PR20 HIV proteases, starting from bound and unbound conformations in each case, were performed.

In silico and in vitro screening to identify structurally diverse non-azole CYP51 inhibitors as potent antifungal agent

Aarti Singh, Sarvesh Kumar Paliwal [Banasthali University], Mukta Sharma, Anupama Mittal, Swapnil Sharma, Jai Prakash Sharma

J. Mol.Graph. and Mod., **63**, 1-7, 2016.

The problem of resistance to azole class of antifungals is a serious cause of concern to the medical fraternity and thus there is an urgent need to identify non-azole scaffolds with high affinity for lanosterol 14 α -demethylase (CYP51). In view of this we have attempted to identify novel non-azole CYP51 inhibitors through the application of pharmacophore based virtual screening and in vitro evaluation. A rigorously validated pharmacophore model comprising of 2 hydrogen bond acceptor and 2 hydrophobic features has been developed and used to mine NCI database.

An in-silico approach aimed to clarify the role of Y181C and K103N HIV-1 reverse transcriptase mutations versus Indole Aryl Sulphones

Alberto Massarotti, Antonio Coluccia [Sapienza Università di Roma]

J. Mol.Graph. and Mod., **63**, 49-56, 2016.

The emergence of HIV-1 drugs resistant strains remains of pivotal interest in relation to drugs development. Non nucleoside reverse transcriptase inhibitors proven to be very effective versus HIV-1 wild type but, with the only exception of diarylpyrimidines (e.g., etravirine, **1**), were featured by high-level resistance versus mutated RT. The effects of two of the most clinically relevant RT mutations (Y181C; K103N) were studied by a computational approach.

Medicinal Chemistry and Drug Design (Cont'd)

A systematic methodology for large scale compound screening: A case study on the discovery of novel S1PL inhibitors

Utku Deniz, Elif Ozkirimli, Kutlu O. Ulgen [Bogazici University]

J. Mol.Graph. and Mod., **63**, 110-124, 2016.

Decrease in sphingosine 1-phosphate (S1P) concentration induces migration of pathogenic T cells to the blood stream, disrupts the CNS and it is implicated in multiple sclerosis (MS), a progressive inflammatory disorder of the central nervous system (CNS), and Alzheimer's disease (AD). A promising treatment alternative for MS and AD is inhibition of the activity of the microsomal enzyme sphingosine 1-phosphate lyase (S1PL), which degrades intracellular S1P. This report describes an integrated systematic approach comprising virtual screening, molecular docking, substructure search and molecular dynamics simulation to discover novel S1PL inhibitors.

Energy-Based Pharmacophore and Three-Dimensional Quantitative Structure–Activity Relationship (3D-QSAR) Modeling Combined with Virtual Screening To Identify Novel Small-Molecule Inhibitors of Silent Mating-Type Information Regulation 2 Homologue 1 (SIRT1)

Venkat Koushik Pulla, Dinavahi Saketh Sriram, Srikant Viswanadha, Dharmarajan Sriram, and Perumal Yogeewari [Birla Institute of Technology and Science–Pilani, Hyderabad Campus]

J.Chem. Infor. and Mod., **56**, 173–187, 2016.

Silent mating-type information regulation 2 homologue 1 (SIRT1), being the homologous enzyme of silent information regulator-2 gene in yeast, has multifaceted functions. It deacetylates a wide range of histone and nonhistone proteins; hence, it has good therapeutic importance. SIRT1 was believed to be overexpressed in many cancers (prostate, colon) and inflammatory disorders (rheumatoid arthritis). Hence, designing inhibitors against SIRT1 could be considered valuable. Both structure-based and ligand-based drug design strategies were employed to design novel inhibitors utilizing high-throughput virtual screening of chemical databases.

Computational insights into the interaction mechanism of triazolyl substituted tetrahydrobenzofuran derivatives with H⁺,K⁺-ATPase at different pH

Hua-Jun Luo [China Three Gorges University], Jun-Zhi Wang, Nian-Yu Huang, Wei-Qiao Deng, Kun Zou

J.Comp.Aided. Mol.des. **30**, 27-37, 2016.

The interaction mechanism of triazolyl substituted tetrahydrobenzofuran derivatives (compound **1** (N, N-Dipropyl-1-(2-phenyl-4,5,6,7-tetrahydrobenzofuran-4-yl)-1H-1,2,3-triazole-4-methanamine) and **2** (1-(2-Phenyl-4,5,6,7-tetrahydrobenzofuran-4-yl)-4-(morpholin-4-ylmethyl)-1H-1,2,3-triazole)) with H⁺,K⁺-ATPase at different pH were studied by induced-fit docking, QM/MM optimization and MM/GBSA binding free energy calculations of two forms (neutral and protonated form) of compounds.

Identification of novel inhibitors for Pim-1 kinase using pharmacophore modeling based on a novel method for selecting pharmacophore generation subsets

Rand Shahin [Zarqa University], Lubna Swellmeen, Omar Shaheen, Nour Aboalhaja, Maha Habash

J.Comp.Aided. Mol.des. **30**, 39-68, 2016.

Targeting Proviral integration-site of murine Moloney leukemia virus 1 kinase, hereafter called Pim-1 kinase, is a promising strategy for treating different kinds of human cancer. Headed for this a total list of 328 formerly reported Pim-1 kinase inhibitors has been explored and divided based on the pharmacophoric features of the most active molecules into 10 subsets projected to represent potential active binding manners accessible to ligands within the binding pocket of Pim-1 kinase. Discovery Studio 4.1 (DS 4.1) was employed to detect potential pharmacophoric active binding manners anticipated by Pim-1 Kinase inhibitors.

Quantitative Structure-Activity Relations

Molecular modeling studies, synthesis and biological evaluation of dabigatran analogues as thrombin inhibitors

Ming-Hui Dong, Hai-Feng Chen, Yu-Jie Ren [Shanghai Institute of Technology], Fang-Ming Shao

Bioorg. and Med. Chem., **24**, 73-84, 2016

In this work, 48 thrombin inhibitors based on the structural scaffold of dabigatran were analyzed using a combination of molecular modeling techniques. We generated three-dimensional quantitative structure-activity relationship (3D-QSAR) models based on three alignments for both comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) to highlight the structural requirements for thrombin protein inhibition. In addition to the 3D-QSAR study, Topomer CoMFA model also was established with a higher leave-one-out cross-validation q^2 and a non-cross-validation r^2 , which suggest that the three models have good predictive ability.

Host-Guest Systems

Insights into Unfolded Proteins from the Intrinsic ϕ/ψ Propensities of the AAXAA Host-Guest Series

Clare-Louise Towse, Jiri Vymetal, Jiri Vondrasek, Valerie Daggett [University of Washington, Seattle]

Biophysical Journal., **110**, 348-361, 2016.

Various host-guest peptide series are used by experimentalists as reference conformational states. One such use is as a baseline for random-coil NMR chemical shifts. Comparison to this random-coil baseline, through secondary chemical shifts, is used to infer protein secondary structure. Here, we use molecular dynamics simulations of an alanine-based host-guest peptide series (AAXAA) as a model of unfolded and denatured states to examine the intrinsic propensities of the amino acids.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Hammock: a hidden Markov model-based peptide clustering algorithm to identify protein-interaction consensus motifs in large datasets

Adam Krejci, Ted R. Hupp, Matej Lexa, Borivoj Vojtesek, and Petr Muller [Masaryk Memorial Cancer Institute]

Bioinformatics. **32**, 9-16, 2016.

Proteins often recognize their interaction partners on the basis of short linear motifs located in disordered regions on proteins' surface. Experimental techniques that study such motifs use short peptides to mimic the structural properties of interacting proteins. The software tool presented in this article is able to rapidly identify multiple clusters of sequences carrying shared specificity motifs in massive datasets from various sources and generate multiple sequence alignments of identified clusters. The method was applied on a previously published smaller dataset containing distinct classes of ligands for SH3 domains, as well as on a new, an order of magnitude larger dataset containing epitopes for several monoclonal antibodies.

Bioinformatics and Cheminformatics (Cont'd)

Rust-Bio: a fast and safe bioinformatics library

Johannes Köster [Dana-Farber Cancer Institute]

Bioinformatics. **32**, 444-446, 2016.

We present Rust-Bio, the first general purpose bioinformatics library for the innovative Rust programming language. Rust-Bio leverages the unique combination of speed, memory safety and high-level syntax offered by Rust to provide a fast and safe set of bioinformatics algorithms and data structures with a focus on sequence analysis.

FALCON@home: a high-throughput protein structure prediction server based on remote homologue recognition

Chao Wang, Haicang Zhang, Wei-Mou Zheng, Dong Xu, Jianwei Zhu, Bing Wang, Kang Ning, Shiwei Sun, Shuai Cheng Li, and Dongbo Bu [Chinese Academy of Sciences, Beijing]

Bioinformatics. **32**, 462-464, 2016.

The protein structure prediction approaches can be categorized into template-based modeling (including homology modeling and threading) and free modeling. However, the existing threading tools perform poorly on remote homologous proteins. In this study, we presented FALCON@home as a protein structure prediction server focusing on remote homologue identification. The design of FALCON@home is based on the observation that a structural template, especially for remote homologous proteins, consists of conserved regions interweaved with highly variable regions. We implemented FALCON@home using the Berkeley Open Infrastructure of Network Computing (BOINC) volunteer computing protocol.

SpringSaLaD: A Spatial, Particle-Based Biochemical Simulation Platform with Excluded Volume

Paul J. Michalski [University of Connecticut Health Center], Leslie M. Loew

Biophysical Journal., **110**, 523-529, 2016.

We introduce Springs, Sites, and Langevin Dynamics (SpringSaLaD), a comprehensive software platform for spatial, stochastic, particle-based modeling of biochemical systems. SpringSaLaD models biomolecules in a coarse-grained manner as a group of linked spherical sites with excluded volume. This mesoscopic approach bridges the gap between highly detailed molecular dynamics simulations and the various methods used to study network kinetics and diffusion at the cellular level. SpringSaLaD is a standalone tool that supports model building, simulation, visualization, and data analysis, all through a user-friendly graphical user interface that should make it more accessible than tools built into more comprehensive molecular dynamics infrastructures.

LEADS-PEP: A Benchmark Data Set for Assessment of Peptide Docking Performance

Alexander Sebastian Hauser and Björn Windshügel [Fraunhofer Institute for Molecular Biology and Applied Ecology IME]

J.Chem. Infor. and Mod., **56**, 188–200, 2016.

With increasing interest in peptide-based therapeutics also the application of computational approaches such as peptide docking has gained more and more attention. In order to assess the suitability of docking programs for peptide placement and to support the development of peptide-specific docking tools, an independently constructed benchmark data set is urgently needed. Here we present the LEADS-PEP benchmark data set for assessing peptide docking performance.

Bioinformatics and Cheminformatics (Cont'd)

General Purpose 2D and 3D Similarity Approach to Identify hERG Blockers

Patric Schyman, Ruifeng Liu, and Anders Wallqvist [U.S. Army Medical Research and Materiel Command]

J.Chem. Infor. and Mod., **56**, 213–222, 2016.

Screening compounds for human ether-à-go-go-related gene (hERG) channel inhibition is an important component of early stage drug development and assessment. In this study, we developed a high-confidence (p-value < 0.01) hERG prediction model based on a combined two-dimensional (2D) and three-dimensional (3D) modeling approach. We developed a 3D similarity conformation approach (SCA) based on examining a limited fixed number of pairwise 3D similarity scores between a query molecule and a set of known hERG blockers. By combining 3D SCA with 2D similarity ensemble approach (SEA) methods, we achieved a maximum sensitivity in hERG inhibition prediction with an accuracy not achieved by either method separately.

Protein Sequence Analysis and Alignment

A multi-objective optimization approach accurately resolves protein domain architectures

J.S. Bernardes, F.R.J. Vieira, G. Zaverucha, and A. Carbone [Sorbonne Universités]

Bioinformatics. **32**, 345-353, 2016.

Given a protein sequence and a number of potential domains matching it, what are the domain content and the most likely domain architecture for the sequence? This problem is of fundamental importance in protein annotation, constituting one of the main steps of all predictive annotation strategies. We developed DAMA (Domain Annotation by a Multi-objective Approach), a novel approach that identifies architectures through a multi-objective optimization algorithm combining scores of domain matches, previously observed multi-domain co-occurrence and domain overlapping.

Protein Conformational Analysis

Direct Calculation of Protein Fitness Landscapes through Computational Protein Design

Loretta Au [The University of Chicago], David F. Green

Biophysical Journal., **110**, 75-84, 2016.

Naturally selected amino-acid sequences or experimentally derived ones are often the basis for understanding how protein three-dimensional conformation and function are determined by primary structure. Such sequences for a protein family comprise only a small fraction of all possible variants, however, representing the fitness landscape with limited scope. Explicitly sampling and characterizing alternative, unexplored protein sequences would directly identify fundamental reasons for sequence robustness (or variability), and we demonstrate that computational methods offer an efficient mechanism toward this end, on a large scale.

Protein Conformational Analysis (Cont'd)

DIRECT-ID: An automated method to identify and quantify conformational variations—application to β_2 -adrenergic GPCR

Sirish Kaushik Lakkaraju, Justin A. Lemkul, Jing Huang and Alexander D. MacKerell Jr. [University of Maryland Baltimore]

J. Comp. Chem., **37**, 416–425, 2016.

The conformational dynamics of a macromolecule can be modulated by a number of factors, including changes in environment, ligand binding, and interactions with other macromolecules, among others. We present a method that quantifies the differences in macromolecular conformational dynamics and automatically extracts the structural features responsible for these changes. Given a set of MD simulations of a macromolecule, the norms of the differences in covariance matrices are calculated for each pair of trajectories. A matrix of these norms thus quantifies the differences in conformational dynamics across the set of simulations.

Convergence of Molecular Dynamics Simulation of Protein Native States: Feasibility vs Self-Consistency Dilemma

Lucas Sawle and Kingshuk Ghosh [University of Denver, Denver]

J. Chem. Theor. and Comp, **12**, 861–869, 2016.

All-atom molecular dynamics simulations need convergence tests to evaluate the quality of data. The notion of “true” convergence is elusive, and one can only hope to satisfy self-consistency checks (SCC). There are multiple SCC criteria, and their assessment of all-atom simulations of the native state for real globular proteins is sparse. Here, we present a systematic study of different SCC algorithms, both in terms of their ability to detect the lack of self-consistency and their computational demand, for the all-atom native state simulations of four globular proteins (CSP, CheA, CheW, and BPTI).

Long-Range Conformational Response of a PDZ Domain to Ligand Binding and Release: A Molecular Dynamics Study

Cheng Lu, Volker Knecht, and Gerhard Stock [Albert Ludwigs University]

J. Chem. Theor. and Comp, **12**, 870–878, 2016.

The binding of a ligand to a protein may induce long-range structural or dynamical changes in the biomacromolecule even at sites physically well separated from the binding pocket. A system for which such behavior has been widely discussed is the PDZ2 domain of human tyrosine phosphatase 1E. Here, we present results from equilibrium trajectories of the PDZ2 domain in the free and ligand-bound state, as well as nonequilibrium simulations of the relaxation of PDZ2 after removal of its peptide ligand. The study reveals changes in inter-residue contacts, backbone dihedral angles, and C_α positions upon ligand release.

β -Hairpin Crowding Agents Affect α -Helix Stability in Crowded Environments

Bryanne Macdonald, Shannon McCarley, Sundus Noeen, and Alan E. van Giessen [Mount Holyoke College, South Hadley]

J. Phys. Chem. B., **120**, 650–659, 2016.

The dense, heterogeneous cellular environment is known to affect protein stability. It is now recognized that attractive “quinary” interactions with other biomacromolecules in the cell, referred to as the crowding agents, play a significant role in determining the stability of the protein of interest or test protein. These attractive interactions can reduce or overcome the stabilizing effect of the excluded volume of the crowding agents. We use molecular simulation to investigate the roles played by hydrophobic interactions and hydrogen bonding between a small helical test protein and equally sized crowding agent proteins in a fixed β -hairpin configuration.

Protein Conformational Analysis (Cont'd)

Comparison of the Conformations of KRAS Isoforms, K-Ras4A and K-Ras4B, Points to Similarities and Significant Differences

Mayukh Chakrabarti, Hyunbum Jang, and Ruth Nussinov
[Frederick National Laboratory for Cancer Research]

J. Phys. Chem. B., **120**, 667–679, 2016.

Human HRAS, KRAS, and NRAS genes encode four isoforms of Ras, a p21 GTPase. Mutations in KRAS account for the majority of RAS-driven cancers. The KRAS has two splice variants, K-Ras4A and K-Ras4B. Due to their reversible palmitoylation, K-Ras4A and N-Ras have bimodal signaling states. K-Ras4A and K-Ras4B differ in four catalytic domain residues (G151R/D153E/K165Q/H166Y) and in their disordered C-terminal hypervariable region (HVR). In K-Ras4A, the HVR is not as strongly positively charged as in K-Ras4B (+6e vs +9e). Here, we performed all-atom molecular dynamics simulations to elucidate isoform-specific differences between the two splice variants.

Conformational fluctuations of the AXH monomer of Ataxin-1

Gianvito Grasso, Marco A. Deriu [Università Della Svizzera Italiana], Jack A. Tuszynski, Diego Gallo, Umberto Morbiducci and Andrea Danani

Proteins: Stru. Fun. & Bioinf., **84**, 52–59, 2016.

In this paper, we report the results of molecular dynamics simulations of AXH monomer of Ataxin-1. The AXH domain plays a crucial role in Ataxin-1 aggregation, which accompanies the initiation and progression of Spinocerebellar ataxia type 1. Our simulations involving both classical and replica exchange molecular dynamics, followed by principal component analysis of the trajectories obtained, reveal substantial conformational fluctuations of the protein structure, especially in the N-terminal region.

Protein Structure Analysis

Fast and accurate non-sequential protein structure alignment using a new asymmetric linear sum assignment heuristic

Peter Brown, Wayne Pullan, Yuedong Yang, and Yaoqi Zhou
[Griffith University]

Bioinformatics. **32**, 370–377, 2016.

The three dimensional tertiary structure of a protein at near atomic level resolution provides insight alluding to its function and evolution. As protein structure decides its functionality, similarity in structure usually implies similarity in function. As such, structure alignment techniques are often useful in the classifications of protein function. The performance of SPalignNS was evaluated against existing sequential and non-sequential structure alignment methods by performing trials with commonly used datasets.

Protein Dynamics

Unit cell structure of water-filled monoolein in inverted hexagonal mesophase in the presence of incorporated tricaprylin and entrapped lysozyme

Vesselin Kolev [The Wolfson Department of Chemical Engineering], Anela Ivanova, Galia Madjarova, Abraham Aserin, Nissim Garti

Eur.Biophy., 45, 99-112, 2016.

Molecular dynamics (MD) was employed by means of a specific simulation protocol to investigate the equilibrium structure at 25 °C of the hexagonal inverted (H_{II}) mesophase composed from water, 1-monoolein (GMO), and tricaprylin, with or without entrapped lysozyme. Based on robust and fast MD simulations, the study provides a comprehensive analysis and visualization of the local structure of H_{II} mesophase containing admixtures. The most important physical insight is the possibility to observe the strong self-recovery capacity of the GMO layer, which allows the H_{II} mesophase tubes to reorganize and host lysozyme molecules with a size bigger than the diameter of the water channel.

Conserved Hydration Sites in Pin1 Reveal a Distinctive Water Recognition Motif in Proteins

Arghya Barman, Crystal Smitherman, Michael Souffrant, Giovanni Gadda, and Donald Hamelberg [Georgia State University, Atlanta]

J.Chem. Infor. and Mod., 56, 139–147, 2016.

Structurally conserved water molecules are important for biomolecular stability, flexibility, and function. X-ray crystallographic studies of Pin1 have resolved a number of water molecules around the enzyme, including two highly conserved water molecules within the protein. We investigate the significance of these structurally conserved water molecules in the catalytic domain of Pin1 using molecular dynamics (MD) simulations, free energy calculations, analysis of X-ray crystal structures, and circular dichroism (CD) experiments.

Analysis of Multidomain Protein Dynamics

Amitava Roy [Rocky Mountain Laboratories, NIAID], Duy P. Hua, and Carol Beth Post

J. Chem. Theor. and Comp., 12, 274–280, 2016.

Proteins with a modular architecture of multiple domains connected by linkers often exhibit diversity in the relative positions of domains, while the domain tertiary structure remains unchanged. The biological function of these modular proteins, or the regulation of their activity, depends on the variation in domain orientation and separation. Accordingly, careful characterization of interdomain motion and correlated fluctuations of multidomain systems is relevant for understanding the functional behavior of modular proteins. Molecular dynamics (MD) simulations provides a powerful approach to study these motions in atomic detail.

An Updated Test of AMBER Force Fields and Implicit Solvent Models in Predicting the Secondary Structure of Helical, β -Hairpin, and Intrinsically Disordered Peptides

Irene Maffucci and Alessandro Contini [Università degli Studi di Milano]

J. Chem. Theor. and Comp., 12, 714–727, 2016.

Replica exchange molecular dynamics simulations were performed to test the ability of six AMBER force fields and three implicit solvent models of predicting the native conformation of two helical peptides, three β -hairpins, and three intrinsically disordered peptides. Although a combination of the force field and implicit solvation models able to accurately predict the native structure of all the considered peptides was not identified, we found that the GB-Neck2 model seems to well compensate for some of the conformational biases showed by ff96 and ff99SB/ildn/ildn- ϕ .

Protein Dynamics (Cont'd)

Multiscale Model for the Assembly Kinetics of Protein Complexes

Zhong-Ru Xie, Jiawen Chen, and Yinghao Wu [Albert Einstein College of Medicine]

J. Phys. Chem. B., **120**, 621–632, 2016.

The assembly of proteins into high-order complexes is a general mechanism for these biomolecules to implement their versatile functions in cells. Natural evolution has developed various assembling pathways for specific protein complexes to maintain their stability and proper activities. Previous studies have provided numerous examples of the misassembly of protein complexes leading to severe biological consequences. We developed a new multiscale modeling framework. This framework combines a lower-resolution rigid-body-based simulation with a higher-resolution α -based simulation method so that protein complexes can be assembled with both structural details and computational efficiency.

Molecular dynamics simulations elucidate the mode of protein recognition by Skp1 and the F-box domain in the SCF complex

Sarath Chandra Dantu, Nitin Nathubhai Kachariya and Ashutosh Kuma [Indian Institute of Technology Bombay]

Proteins: Stru. Fun. & Bioinf., **84**, 159–171, 2016.

Polyubiquitination of the target protein by a ubiquitin transferring machinery is key to various cellular processes. E3 ligase Skp1-Cul1-F-box (SCF) is one such complex which plays crucial role in substrate recognition and transfer of the ubiquitin molecule. Previous computational studies have focused on S-phase kinase-associated protein 2 (Skp2), cullin, and RING-finger proteins of this complex, but the roles of the adapter protein Skp1 and F-box domain of Skp2 have not been determined. Using sub-microsecond molecular dynamics simulations of full-length Skp1, unbound Skp2, Skp2-Cks1 (Cks1: Cyclin-dependent kinases regulatory subunit 1), Skp1-Skp2, and Skp1-Skp2-Cks1 complexes, we have elucidated the function of Skp1 and the F-box domain of Skp2.

Redesigning the stereospecificity of tyrosyl-tRNA synthetase

Thomas Simonson, Shixin Ye-Lehmann, Zoltan Palmai, Najette Amara, Sandra Wydau-Dematteis, Erwan Bigan, Karen Druart, Clara Moch and Pierre Plateau [Ecole Polytechnique, Palaiseau]

Proteins: Stru. Fun. & Bioinf., **84**, 240–253, 2016.

d-Amino acids are largely excluded from protein synthesis, yet they are of great interest in biotechnology. Unnatural amino acids have been introduced into proteins using engineered aminoacyl-tRNA synthetases (aaRSs), and this strategy might be applicable to d-amino acids. Several aaRSs can aminoacylate their tRNA with a d-amino acid; of these, tyrosyl-tRNA synthetase (TyrRS) has the weakest stereospecificity. We use computational protein design to suggest active site mutations in *Escherichia coli* TyrRS that could increase its d-Tyr binding further, relative to l-Tyr. The mutations selected all modify one or more sidechain charges in the Tyr binding pocket.

Protein Dynamics (Cont'd)

Cy-preds: An algorithm and a web service for the analysis and prediction of cysteine reactivity

İnanç Soylu and Stefano M. Marino [Akdeniz University, Antalya]

Proteins: Stru. Fun. & Bioinf., **84**, 278–291, 2016.

Cysteine (Cys) is a critically important amino acid, serving a variety of functions within proteins including structural roles, catalysis, and regulation of function through post-translational modifications. Predicting which Cys residues are likely to be reactive is a very sought after feature. Few methods are currently available for the task, either based on evaluation of physicochemical features (e.g., pKa and exposure) or based on similarity with known instances. In this study, we developed an algorithm (named HAL-Cy) which blends previous work with novel implementations to identify reactive Cys from nonreactive.

Free Energy Calculations

Investigation of the free energy profiles of amantadine and rimantadine in the AM2 binding pocket

Hung Van Nguyen, Hieu Thanh Nguyen, Ly Thi Le [for Computational Science and Technology, Ho Chi Minh City]

Eur.Biophy., **45**, 63-70, 2016.

The purpose of this work was to study the mechanism of drug resistance of M2 channel proteins by analyzing the interactions between the drugs amantadine and rimantadine and M2 channel proteins (including the wild type and the three mutants V27A, S31N, and G34A) and the drug binding pathways, by use of a computational approach. Our results showed that multiple drug-binding sites were present in the M2 channel, and the trajectory of the drugs through the M2 channel was determined. A novel method was developed to investigate of free energy profiles of the ligand–protein complexes.

Ligand Binding/Docking

T-Cell Receptor Binding Affects the Dynamics of the Peptide/MHC-I Complex

Bernhard Knapp [University of Oxford] and Charlotte M. Deane

J.Chem. Infor. and Mod., **56**, 46–53, 2016.

The recognition of peptide/MHC by T-cell receptors is one of the most important interactions in the adaptive immune system. A large number of computational studies have investigated the structural dynamics of this interaction. However, to date only limited attention has been paid to differences between the dynamics of peptide/MHC with the T-cell receptor bound and unbound. Here we present the first large-scale molecular dynamics simulation study of this type investigating HLA-B*08:01 in complex with the Epstein–Barr virus peptide FLRGRAYGL and all possible single-point mutations (n = 172).

Ligand Binding / Docking (Cont'd)

H274Y's Effect on Oseltamivir Resistance: What Happens Before the Drug Enters the Binding Site

Muhammad Yusuf, Nornisah Mohamed, Suriyati Mohamad, Dusanka Janezic, K. V. Damodaran, and Habibah A. Wahab [Universiti Sains Malaysia]

J.Chem. Infor. and Mod., **56**, 82–100, 2016.

Increased reports of oseltamivir (OTV)-resistant strains of the influenza virus, such as the H274Y mutation on its neuraminidase (NA), have created some cause for concern. Many studies have been conducted in the attempt to uncover the mechanism of OTV resistance in H274Y NA. However, most of the reported studies on H274Y focused only on the drug-bound system, so the direct effects of the mutation on NA itself prior to drug binding still remain unclear. Therefore, MD simulations of NA in apo form, followed by principal component analysis and interaction energy calculations, were performed to investigate the structural changes of the NA binding site as a result of the H274Y mutation.

Combination of Ambiguous and Unambiguous Data in the Restraint-driven Docking of Flexible Peptides with HADDOCK: The Binding of the Spider Toxin PcTx1 to the Acid Sensing Ion Channel (ASIC) 1a

Evelyn Deplazes, Josephine Davies, Alexandre M. J. J. Bonvin, Glenn F. King, and Alan E. Mark [The University of Queensland]

J.Chem. Infor. and Mod., **56**, 127–138, 2016.

Peptides that bind to ion channels have attracted much interest as potential lead molecules for the development of new drugs and insecticides. However, the structure determination of large peptide-channel complexes using experimental methods is challenging. Thus structural models are often derived from combining experimental information with restraint-driven docking approaches. Using the complex formed by the venom peptide PcTx1 and the acid sensing ion channel (ASIC) 1a as a case study, we have examined the effect of different combinations of restraints and input structures.

Discovery of Subtype Selective Janus Kinase (JAK) Inhibitors by Structure-Based Virtual Screening

Dávid Bajusz, György G. Ferenczy, and György M. Keserű [Hungarian Academy of Sciences]

J.Chem. Infor. and Mod., **56**, 234–247, 2016.

Janus kinase inhibitors represent a promising opportunity for the pharmaceutical intervention of various inflammatory and oncological indications. Subtype selective inhibition of these enzymes, however, is still a very challenging goal. In this study, a novel, customized virtual screening protocol was developed with the intention of providing an efficient tool for the discovery of subtype selective JAK2 inhibitors. The screening protocol involves protein ensemble-based docking calculations combined with an Interaction Fingerprint (IFP) based scoring scheme for estimating ligand affinities and selectivities, respectively.

SIENA: Efficient Compilation of Selective Protein Binding Site Ensembles

Stefan Bietz and Matthias Rarey [University of Hamburg]

J.Chem. Infor. and Mod., **56**, 248–259, 2016.

Structural flexibility of proteins has an important influence on molecular recognition and enzymatic function. In modeling, structure ensembles are therefore often applied as a valuable source of alternative protein conformations. However, their usage is often complicated by structural artifacts and inconsistent data annotation. Here, we present SIENA, a new computational approach for the automated assembly and preprocessing of protein binding site ensembles. Starting with an arbitrarily defined binding site in a single protein structure, SIENA searches for alternative conformations of the same or sequentially closely related binding sites.

Ligand Binding / Docking (Cont'd)

Binding of Disordered Peptides to Kelch: Insights from Enhanced Sampling Simulations

Trang Nhu Do, Wing-Yiu Choy, and Mikko Karttunen
[University of Waterloo]

J. Chem. Theor. and Comp., **12**, 395–404, 2016.

Keap1 protein plays an essential role in regulating cellular oxidative stress response and is a crucial binding hub for multiple proteins, several of which are intrinsically disordered proteins (IDP). Among Kelch's IDP binding partners, NRF2 and PTMA are the two most interesting cases. They share a highly similar binding motif; however, NRF2 binds to Kelch with a binding affinity of approximately 100-fold higher than that of PTMA. In this study, we perform an exhaustive sampling composed of 6 μ s well-tempered metadynamics and 2 μ s unbiased molecular dynamics (MD) simulations aiming at characterizing the binding mechanisms and structural properties of these two peptides.

New insights into the stereochemical requirements of the bradykinin B₂ receptor antagonists binding

Cecylia S. Lupala, Patricia Gomez-Gutierrez, Juan J. Perez
[Universitat Politècnica de Catalunya]

J. Comp. Aided. Mol. des. **30**, 85-101, 2016.

Bradykinin (BK) is a member of the kinin family, released in response to inflammation, trauma, burns, shock, allergy and some cardiovascular diseases, provoking vasodilatation and increased vascular permeability among other effects. The goal of the present work is to carry out a structure–activity study of BK B₂ antagonism, taking into account the stereochemical features of diverse non-peptide antagonists and the way these features translate into ligand anchoring points to complementary regions of the receptor, through the analysis of the respective ligand-receptor complex.

Dynamics and allostery of the ionotropic glutamate receptors and the ligand binding domain

Dror Tobi [Ariel University, Ariel]

Proteins: Stru. Fun. & Bioinf., **84**, 267–277, 2016.

The dynamics of the ligand-binding domain (LBD) and the intact ionotropic glutamate receptor (iGluR) were studied using Gaussian Network Model (GNM) analysis. The dynamics of LBDs with various allosteric modulators is compared using a novel method of multiple alignment of GNM modes of motion. The analysis reveals that allosteric effectors change the dynamics of amino acids at the upper lobe interface of the LBD dimer as well as at the hinge region between the upper- and lower- lobes.

Enzyme Catalysis

Insight into the interactive residues between two domains of human somatic Angiotensin-converting enzyme and Angiotensin II by MM-PBSA calculation and steered molecular dynamics simulation

Shan-shan Guan, Wei-wei Han, Hao Zhang, Song Wang & Ya-ming Shan [Jilin University]

J. Biomol. Stru. and Dyn., **34**, 15-28, 2016.

Angiotensin-converting enzyme (ACE), a membrane-bound zinc metallopeptidase, catalyzes the formation of Angiotensin-II (AngII) and the deactivation of bradykinin in the renin–angiotensin–aldosterone and kallikrein–kinin systems. As a hydrolysis product of ACE, AngII is regarded as an inhibitor and displays stronger competitive inhibition in the C-domain than the N-domain of ACE. In this work, molecular docking, Molecular Mechanics/Poisson–Boltzmann Surface Area calculation, and steered molecular dynamics (SMD) are applied to explore the structures and interactions in the binding or unbinding of AngII with the two domains of human somatic ACE.

Prediction of binding modes and affinities of 4-substituted-2,3,5,6-tetrafluorobenzenesulfonamide inhibitors to the carbonic anhydrase receptor by docking and ONIOM calculations

Pabitra Narayan Samanta, Kalyan Kumar Das [Jadavpur University]

J. Mol.Graph. and Mod., **63**, 38-48, 2016.

Inhibition activities of a series of 4-substituted-2,3,5,6-tetrafluorobenzenesulfonamides against the human carbonic anhydrase II (HCAII) enzyme have been explored by employing molecular docking and hybrid QM/MM methods. The docking protocol has been employed to assess the best pose of each ligand in the active site cavity of the enzyme, and probe the interactions with the amino acid residues. The docking calculations reveal that the inhibitor binds to the catalytic Zn²⁺ site through the deprotonated sulfonamide nitrogen atom by making several hydrophobic and hydrogen bond interactions with the side chain residues depending on the substituted moiety.

LOX1 inhibition with small molecules

Chrysoula Gousiadou [Technical University of Denmark], Irene Kouskoumvekak

J. Mol.Graph. and Mod., **63**, 99-109, 2016.

Lipoxygenases (LOXs) are nonheme, iron-containing dioxygenases that catalyze the dioxygenation of polyunsaturated fatty acids and are widely distributed among plant and animal species. Human LOXs, now identified as key enzymes in the pathogenesis of major disorders, have increasingly drawn the attention as targets and great effort has been made for the discovery and design of suitable inhibitors, to which end both pharmacological and computational methods have been employed. In the present work, using pharmacophore modeling and docking, we attempt to elucidate the inhibition of LOX1 with a new inhibitor, albidoside, an iridoid glucoside isolated from plants of the *Scutellaria* genus.

Enzyme Catalysis (Cont'd)

A fast loop-closure algorithm to accelerate residue matching in computational enzyme design

Jing Xue, Xiaoqiang Huang, Min Lin, Yushan Zhu [Tsinghua University]

J. Mol.Mod., **22**, 49, 2016.

Constructing an active site on an inert scaffold is still a challenge in chemical biology. Herein, we describe the incorporation of a Newton-direction-based fast loop-closure algorithm for catalytic residue matching into our enzyme design program ProdaMatch. This was developed to determine the sites and geometries of the catalytic residues as well as the position of the transition state with high accuracy in order to satisfy the geometric constraints on the interactions between catalytic residues and the transition state.

The mechanism of the effect of U18666a on blocking the activity of 3 β -hydroxysterol Δ -24-reductase (DHCR24): molecular dynamics simulation study and free energy analysis

Xiaoping Quan, Xiuqiang Chen, Deliang Sun, Bo Xu, Linlin Zhao, Xiaoqian Shi, Hongsheng Liu, Bing Gao, Xiuli Lu [Liaoning University]

J. Mol.Mod., **22**, 46, 2016.

DHCR24 encodes 3 β -hydroxysterol- Δ ²⁴-reductase (DHCR24) catalyzing the cholesterol synthesis from desmosterol using the flavin adenine dinucleotide (FAD) as a co-factor. It is generally accepted that U18666a inhibits the reductase activity of DHCR24, but the detailed mechanism remains elusive. To explore the mechanism of the inhibitory effect of U18666a on DHCR24, we performed molecular dynamics (MD) simulations of two complexes including complexes of DHCR24-FAD-desmosterol enzymatic reactive components with and without the inhibitor U18666a.

Unraveling Binding Effects of Cobalt(II) Sepulchrates with the Monooxygenase P450 BM-3 Heme Domain Using Molecular Dynamics Simulations

Rajni Verma, Ulrich Schwaneberg, Dirk Holtmann, and Danilo Roccatano [University of Lincoln]

J. Chem. Theor. and Comp., **12**, 353–363, 2016.

One of the major limitations to exploit enzymes in industrial processes is their dependence on expensive reduction equivalents like NADPH to drive their catalytic cycle. Soluble electron-transfer (ET) mediators like cobalt(II) sepulchrates have been proposed as a cost-effective alternative to shuttle electrons between an inexpensive electron source and an enzyme's redox center. The interactions of these molecules with enzymes have not yet been elucidated at the molecular level. Herein, molecular dynamics simulations are performed to understand the binding and ET mechanism of the cobalt(II) sepulchrates with the heme domain of cytochrome P450 BM-3.

Enzyme Catalysis (Cont'd)

Unraveling the distinctive features of hemorrhagic and non-hemorrhagic snake venom metalloproteinases using molecular simulations

Raoni Almeida de Souza, Natalia Díaz, Ronaldo Alves Pinto Nagem, Rafaela Salgado Ferreira, Dimas Suárez [Universidad de Oviedo]

J.Comp.Aided. Mol.des. **30**, 69-83 , 2016.

Snake venom metalloproteinases are important toxins that play fundamental roles during envenomation. They share a structurally similar catalytic domain, but with diverse hemorrhagic capabilities. To understand the structural basis for this difference, we build and compare two dynamical models, one for the hemorrhagic atroxlysin-I from *Bothrops atrox* and the other for the non-hemorrhagic leucurolysin-a from *Bothrops leucurus*. The analysis of the extended molecular dynamics simulations shows some changes in the local structure, flexibility and surface determinants that can contribute to explain the different hemorrhagic activity of the two enzymes.

Protein-Protein Interactions

Computational probing protein-protein interactions targeting small molecules

Yong-Cui Wang, Shi-Long Chen, Nai-Yang Deng, and Yong Wang [Chinese Academy of Sciences]

Bioinformatics. **32**, 226-234, 2016.

With the booming of interactome studies, a lot of interactions can be measured in a high throughput way and large scale datasets are available. Here, we propose a machine learning method to predict PPI targets in a genomic-wide scale. Specifically, we develop a computational method, named as PrePPItar, to Predict PPIs as drug targets by uncovering the potential associations between drugs and PPIs. First, we survey the databases and manually construct a gold-standard positive dataset for drug and PPI interactions. This effort leads to a dataset with 227 associations among 63 PPIs and 113 FDA-approved drugs and allows us to build models to learn the association rules from the data.

Target the More Druggable Protein States in a Highly Dynamic Protein-Protein Interaction System

Zuojun Guo, Atli Thorarensen, Jianwei Che, and Li Xing [Pfizer Inc., Cambridge]

J.Chem. Infor. and Mod., **56**, 35-45, 2016.

The proteins of the Bcl-2 family play key roles in the regulation of programmed cell death by controlling the integrity of the outer mitochondrial membrane and the initiation of the apoptosis process. We performed extensive molecular dynamics simulations to investigate the conformational flexibility of the Bcl-x_L protein in both the apo and holo (with Bad peptide and ABT-737) states. The accelerated molecular dynamics method implemented in Amber 14 was used to produce broader conformational sampling of 200 ns simulations.

Structure and Function of Photosystem I-[FeFe] Hydrogenase Protein Fusions: An All-Atom Molecular Dynamics Study

Bradley J. Harris, Xiaolin Cheng, and Paul Frymier [University of Tennessee, Knoxville]

J. Phys. Chem. B., **120**, 599-609, 2016.

All-atom molecular dynamics (MD) simulation was used to study the solution dynamics and protein-protein interactions of protein fusions of photosystem I (PSI) from *Thermosynechococcus elongatus* and an [FeFe]-hydrogenase (FeFe H₂ase) from *Clostridium pasteurianum*, a unique complex capable of photocatalytic hydrogen production. This study involved fusions of these two proteins via dithiol linkers of different length including decanedithiol, octanedithiol, and hexanedithiol, for which experimental data had previously been obtained.

Membrane Proteins and Lipid Peptide Interactions

Thermodynamics calculation of protein–ligand interactions by QM/MM polarizable charge parameters

Jinan Wang, Qiang Shao, Benjamin P. Cossins, Jiye Shi, Kaixian Chen & Weiliang Zhu [Chinese Academy of Sciences]

J. Biomol. Stru. and Dyn., **34**, 163-176, 2016.

The calculation of protein–ligand binding free energy (ΔG) is of great importance for virtual screening and drug design. Molecular dynamics (MD) simulation has been an attractive tool to investigate this scientific problem. However, the reliability of such approach is affected by many factors including electrostatic interaction calculation. Here, we present a practical protocol using quantum mechanics/molecular mechanics (QM/MM) calculations to generate polarizable QM protein charge (QMPC). The calculated QMPC of some atoms in binding pockets was obviously different from that calculated by AMBER ff03, which might significantly affect the calculated ΔG .

DOX: A new computational protocol for accurate prediction of the protein–ligand binding structures

Li Rao, Bo Chi, Yanliang Ren, Yongjian Li, Xin Xu and Jian Wan [Central China Normal University, Wuhan]

J. Comp. Chem., **37**, 336–344, 2016.

Molecular docking techniques have now been widely used to predict the protein–ligand binding modes, especially when the structures of crystal complexes are not available. Most docking algorithms are able to effectively generate and rank a large number of probable binding poses. However, it is hard for them to accurately evaluate these poses and identify the most accurate binding structure. In this study, we first examined the performance of some docking programs, based on a testing set made of 15 crystal complexes with drug statins for the human 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR).

Protein:Ligand binding free energies: A stringent test for computational protein design

Karen Druart, Zoltan Palmai, Eyaz Omarjee and Thomas Simonson [Ecole Polytechnique, Palaiseau]

J. Comp. Chem., **37**, 404–415, 2016.

A computational protein design method is extended to allow Monte Carlo simulations where two ligands are titrated into a protein binding pocket, yielding binding free energy differences. These provide a stringent test of the physical model, including the energy surface and sidechain rotamer definition. As a test, we consider tyrosyl-tRNA synthetase (TyrRS), which has been extensively redesigned experimentally. We consider its specificity for its substrate l-tyrosine (l-Tyr), compared to the analogs d-Tyr, p-acetyl-, and p-azido-phenylalanine (ac-Phe, az-Phe).

A MARTINI extension for *Pseudomonas aeruginosa* PAO1 lipopolysaccharide

Brad Van Oosten [Brock University], Thad A. Harroun

J. Mol.Graph. and Mod., **63**, 125-133, 2016.

We report a course-grained, large scale simulation of the outer membrane from *Pseudomonas aeruginosa*. Using the MARTINI force field approach of 4-to-1 atom mapping, we simulate an asymmetrically constructed bilayer with over 1100 rough lipopolysaccharide (LPS) and 3100 16:0-18:1-phosphatidylethanolamine. We achieve 90-fold improvement in computational efficiency on a system much larger than reasonable for all-atom simulation. We also compare a coarse-grained LPS/LPS bilayer simulation with known parameters determined from neutron diffraction.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

The Fragment Molecular Orbital Method Reveals New Insight into the Chemical Nature of GPCR-Ligand Interactions

Alexander Heifetz, Ewa I. Chudyk [Evotec (U.K.) Ltd.], Laura Gleave, Matteo Aldeghi, Vadim Cherezov, Dmitri G. Fedorov, Philip C. Biggin, and Mike J. Bodkin

J.Chem. Infor. and Mod., **56**, 159–172, 2016.

Our interpretation of ligand–protein interactions is often informed by high-resolution structures, which represent the cornerstone of structure-based drug design. However, visual inspection and molecular mechanics approaches cannot explain the full complexity of molecular interactions. Quantum Mechanics approaches are often too computationally expensive, but one method, Fragment Molecular Orbital (FMO), offers an excellent compromise and has the potential to reveal key interactions that would otherwise be hard to detect.

Impact of Surface Water Layers on Protein–Ligand Binding: How Well Are Experimental Data Reproduced by Molecular Dynamics Simulations in a Thermolysin Test Case?

Michael Betz, Tobias Wulsdorf, Stefan G. Krimmer, and Gerhard Klebe [Philipps-University Marburg]

J.Chem. Infor. and Mod., **56**, 223–233, 2016.

Drug binding involves changes of the local water structure around proteins including water rearrangements across surface-solvation layers around protein and ligand portions exposed to the newly formed complex surface. For a series of thermolysin-binding phosphoramidates, we discovered that variations of the partly exposed P2'-substituents modulate binding affinity up to 10 kJ mol⁻¹ with even larger enthalpy/entropy partitioning of the binding signature. The observed profiles cannot be completely explained by desolvation effects. Instead, the quality and completeness of the surface water network wrapping around the formed complexes provide an explanation for the observed structure–activity relationship.

CHARMM-GUI Input Generator for NAMD, GROMACS, AMBER, OpenMM, and CHARMM/OpenMM Simulations Using the CHARMM36 Additive Force Field

Jumin Lee, Xi Cheng, Jason M. Swails, Min Sun Yeom, Peter K. Eastman, Justin A. Lemkul, Shuai Wei, Joshua Buckner, Jong Cheol Jeong, Yifei Qi, Sunhwan Jo, Vijay S. Pande, David A. Case, Charles L. Brooks III, Alexander D. MacKerell Jr., Jeffery B. Klauda, and Wonpil Im [The University of Kansas, Lawrence]

J. Chem. Theor. and Comp., **12**, 405–413, 2016.

Proper treatment of nonbonded interactions is essential for the accuracy of molecular dynamics (MD) simulations, especially in studies of lipid bilayers. The use of the CHARMM36 force field (C36 FF) in different MD simulation programs can result in disagreements with published simulations performed with CHARMM due to differences in the protocols used to treat the long-range and 1–4 nonbonded interactions. In this study, we systematically test the use of the C36 lipid FF in NAMD, GROMACS, AMBER, OpenMM, and CHARMM/OpenMM. A wide range of Lennard-Jones (LJ) cutoff schemes and integrator algorithms were tested to find the optimal simulation protocol to best match bilayer properties of six lipids with varying acyl chain saturation and head groups.

Guanidinium Pairing Facilitates Membrane Translocation

Christoph Allolio [Czech Academy of Sciences], Katarina Baxova, Mario Vazdar, and Pavel Jungwirth

J. Phys. Chem. B., **120**, 143–153, 2016.

Ab initio free energy calculations of guanidinium pairing in aqueous solution confirm the counterintuitive conjecture that the like-charge ion pair is thermodynamically stable. Transferring the guanidinium pair to the inside of a POPC lipid bilayer, like-charge ion pairing is found to occur also inside the membrane defect. It is found to contribute to the nonadditivity of ion transfer, thereby facilitating the presence of ions inside the bilayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

A Microscopic Capacitor Model of Voltage Coupling in Membrane Proteins: Gating Charge Fluctuations in Ci-VSD

Ilsoo Kim and Arie Warshel [University of Southern California]

J. Phys. Chem. B., **120**, 418–432, 2016.

The voltage sensitivity of membrane proteins is reflected in the response of the voltage sensing domains (VSDs) to the changes in membrane potential. This response is implicated in the displacement of positively charged residues, associated with the conformational changes of VSDs. Concomitant with the development of our coarse-graining (CG) model of voltage coupling, we apply our theoretical framework for the treatments of voltage effects in membrane proteins to modeling the VSMP activation, taking the VSDs (Ci-VSD) derived from the *Ciona intestinalis* voltage sensitive phosphatase (Ci-VSP) as a model system. Our CG model reproduces the observed gating charge of Ci-VSD activation in several different perspectives.

Refining the treatment of membrane proteins by coarse-grained models

Igor Vorobyov, Ilsoo Kim, Zhen T. Chu and Arie Warshel [University of Southern California]

Proteins: Stru. Fun. & Bioinf., **84**, 92–117, 2016.

Obtaining a quantitative description of the membrane proteins stability is crucial for understanding many biological processes. However the advance in this direction has remained a major challenge for both experimental studies and molecular modeling. One of the possible directions is the use of coarse-grained models but such models must be carefully calibrated and validated. Here we use a recent progress in benchmark studies on the energetics of amino acid residue and peptide membrane insertion and membrane protein stability in refining our previously developed coarse-grained model.

Protein Folding

The Role of Electrostatic Interactions in Folding of β -Proteins

Caitlin M. Davis and R. Brian Dyer [Emory University, Atlanta]

J. Am. Chem. Soc., **138**, 1456–1464, 2016.

Atomic-level molecular dynamic simulations are capable of fully folding structurally diverse proteins; however, they are limited in their ability to accurately represent electrostatic interactions. Here we have experimentally tested the role of charged residues on stability and folding kinetics of one of the most widely simulated β -proteins, the WW domain. The folding of wild type Pin1 WW domain, which has two positively charged residues in the first turn, was compared to the fast folding mutant FiP35 Pin1, which introduces a negative charge into the first turn.

Protein folds recognized by an intelligent predictor based on evolutionary and structural information

Ngaam J. Cheung, Xue-Ming Ding and Hong-Bin Shen [Shanghai Jiao Tong University]

J. Comp. Chem., **37**, 426–436, 2016.

Protein fold recognition is an important and essential step in determining tertiary structure of a protein in biological science. In this study, a model termed NiRecor is developed for recognizing protein folds based on artificial neural networks incorporated in an adaptive heterogeneous particle swarm optimizer. The main contribution of NiRecor is that it is a data-driven and highly-performing predictor without manually tuning control parameters for different data sets.

Protein Folding (Cont'd)

General Protein Data Bank-Based Collective Variables for Protein Folding

Albert Ardevol [ETH Zurich, USI-Campus], Ferruccio Palazzesi, Gareth A. Tribello, and Michele Parrinello

J. Chem. Theor. and Comp., **12**, 29–35, 2016.

New, automated forms of data analysis are required to understand the high-dimensional trajectories that are obtained from molecular dynamics simulations on proteins. Dimensionality reduction algorithms are particularly appealing in this regard as they allow one to construct unbiased, low-dimensional representations of the trajectory using only the information encoded in the trajectory. The downside of this approach is that a different set of coordinates are required for each different chemical system under study precisely because the coordinates are constructed using information from the trajectory.

Folding Simulations of an α -Helical Hairpin Motif *ata* with Residue-Specific Force Fields

Juan Zeng, Fan Jiang, and Yun-Dong Wu [Peking University Shenzhen Graduate School]

J. Phys. Chem. B., **120**, 33–41, 2016.

α -Helical hairpin (two-helix bundle) is a structure motif composed of two interacting helices connected by a turn or a short loop. It is an important model for protein folding studies, filling the gap between isolated α -helix and larger all- α domains. Here, we present, for the first time, successful folding simulations of an α -helical hairpin. Our RSFF1 and RSFF2 force fields give very similar predicted structures of this *ata* peptide, which is in good agreement with its NMR structure.

Fully Atomistic Simulations of Protein Unfolding in Low Speed Atomic Force Microscope and Force Clamp Experiments with the Help of Boxed Molecular Dynamics

Jonathan J. Booth and Dmitrii V. Shalashilin [University of Leeds]

J. Phys. Chem. B., **120**, 700–708, 2016.

The results of boxed dynamics (BXD) fully atomistic simulations of protein unfolding by atomic force microscopy (AFM) in both force clamp (FC) and velocity clamp (VC) modes are reported. In AFM experiments the unfolding occurs on a time scale which is too long for standard atomistic molecular dynamics (MD) simulations, which are usually performed with the addition of forces which exceed those of experiment by many orders of magnitude. BXD can reach the time scale of slow unfolding and sample the very high free energy unfolding pathway, reproducing the experimental dependence of pulling force against extension and extension against time.

Using Kinetic Network Models To Probe Non-Native Salt-Bridge Effects on α -Helix Folding

Guangfeng Zhou and Vincent A. Voelz [Temple University]

J. Phys. Chem. B., **120**, 926–935, 2016.

Salt-bridge interactions play an important role in stabilizing many protein structures, and have been shown to be designable features for protein design. In this work, we study the effects of non-native salt bridges on the folding of a soluble alanine-based peptide (Fs peptide) using extensive all-atom molecular dynamics simulations performed on the Folding@home distributed computing platform. Using Markov State Models, we show how non-native salt-bridges affect the folding kinetics of Fs peptide by perturbing specific conformational states.

Protein-Nucleic acid Interactions

Effects of MacroH2A and H2A.Z on Nucleosome Dynamics as Elucidated by Molecular Dynamics Simulations

Samuel Bowerman, Jeff Wereszczynski [Illinois Institute of Technology]

Biophysical Journal., **110**, 75-84, 2016.

Eukaryotes tune the transcriptional activity of their genome by altering the nucleosome core particle through multiple chemical processes. In particular, replacement of the canonical H2A histone with the variants macroH2A and H2A.Z has been shown to affect DNA accessibility and nucleosome stability; however, the processes by which this occurs remain poorly understood. In this study, we elucidate the molecular mechanisms of these variants with an extensive molecular dynamics study of the canonical nucleosome along with three variant-containing structures: H2A.Z, macroH2A, and an H2A mutant with macroH2A-like L1 loops.

Diffusive dynamics of DNA unzipping in a nanopore

Anna Stachiewicz [Adam Mickiewicz University] and Andrzej Molski

J. Comp. Chem., **37**, 467–476, 2016.

When an electric field is applied to an insulating membrane, movement of charged particles through a nanopore is induced. The measured ionic current reports on biomolecules passing through the nanopore. In this work, we explored the kinetics of DNA unzipping in a nanopore using our coarse-grained model (Stachiewicz and Molski, *J. Comput. Chem.* 2015, 36, 947). Coarse graining allowed a more detailed analysis for a wider range of parameters than all-atom simulations. Dependence of the translocation mode (unzipping or distortion) on the pore diameter was examined, and the threshold voltages were estimated.

Unravelling Protein–DNA Interactions at Molecular Level: A DFT and NCI Study

J. González, I. Baños, I. León, J. Contreras-García, E. J. Cocinero, A. Lesarri, J. A. Fernández, and J. Millán [Universidad de La Rioja]

J. Chem. Theor. and Comp., **12**, 523–534, 2016.

Histone–DNA interactions were probed computationally at a molecular level, by characterizing the bimolecular clusters constituted by selected amino acid derivatives with polar (asparagine and glutamine), nonpolar (alanine, valine, and isoleucine), and charged (arginine) side chains and methylated pyrimidinic (1-methylcytosine and 1-methylthymine) and puric (9-methyladenine and 9-methylguanine) DNA bases. The computational approach combined different methodologies: a molecular mechanics (MMFFs forced field) conformational search and structural and vibrational density-functional calculations (M06-2X with double and triple- ζ Pople's basis sets).

Probing the Salt Concentration Dependent Nucleobase Distribution in a Single-Stranded DNA–Single-Walled Carbon Nanotube Hybrid with Molecular Dynamics

Soumadwip Ghosh, Nisheet Patel, and Rajarshi Chakrabarti [Indian Institute of Technology, Powai]

J. Phys. Chem. B., **120**, 455–466, 2016.

The hybrids of single-walled carbon nanotube (SWCNT) and single stranded DNA (ssDNA) are novel nanoscale materials having remarkable applications in nanotechnology. The absorption of nucleobases on the surface of a SWCNT depends strongly on the ionic strength of the medium. In this paper, using atomistic molecular dynamics we have shown that at low salt concentration ssDNA wraps on the surface of SWCNT through hydrophobic π – π stacking between the DNA bases and the sp^2 -hybridized carbon atoms of the carbon nanotube.

Nucleic Acids

SHAPE directed RNA folding

Ronny Lorenz, Dominik Luntzer, Ivo L. Hofacker, Peter F. Stadler, and Michael T. Wolfinger [University of Vienna]

Bioinformatics. **32**, 145-147, 2016.

Chemical mapping experiments allow for nucleotide resolution assessment of RNA structure. We demonstrate that different strategies of integrating probing data with thermodynamics-based RNA secondary structure prediction algorithms can be implemented by means of soft constraints. This amounts to incorporating suitable pseudo-energies into the standard energy model for RNA secondary structures. The capability for SHAPE directed RNA folding is part of the upcoming release of the ViennaRNA Package 2.2, for which a preliminary release is already freely available at <http://www.tbi.univie.ac.at/RNA>.

Pseudoknots in RNA folding landscapes

Marcel Kucharík, Ivo L. Hofacker, Peter F. Stadler, and Jing Qin University of Copenhagen]

Bioinformatics. **32**, 187-194, 2016.

The function of an RNA molecule is not only linked to its native structure, which is usually taken to be the ground state of its folding landscape, but also in many cases crucially depends on the details of the folding pathways such as stable folding intermediates or the timing of the folding process itself. To model and understand these processes, it is necessary to go beyond ground state structures. We generalize the BHG framework to include pseudoknotted RNA structures and systematically study the differences in predicted folding behavior depending on whether pseudoknotted structures are allowed to occur as folding intermediates or not.

Evaluating Hydrogen Bonds and Base Stacking of Single, Tandem and Terminal GU Mismatches in RNA with a Mesoscopic Model

Tauanne D. Amarante and Gerald Weber [Universidade Federal de Minas Gerais]

J.Chem. Infor. and Mod., **56**, 101–109, 2016.

Guanine–Uracil (GU) mismatches are crucial to the stability of the RNA double helix and need to be considered in RNA folding algorithms for numerous biotechnological applications. Yet despite its importance, many aspects of GU base pairs are still poorly understood. There is also a lack of parametrization which prevents it to be considered in mesoscopic models. Here, we adapted the mesoscopic Peyrard–Bishop model to deal with context-dependent hydrogen bonds of GU mismatches and calculated the model parameters related to hydrogen bonding and base stacking from available experimental melting temperatures.

Nucleic Acids (Cont'd)

General Protein Data Bank-Based Collective Variables for Protein Folding

Albert Ardevol [ETH Zurich, USI-Campus], Ferruccio Palazzesi, Gareth A. Tribello, and Michele Parrinello

J. Chem. Theor. and Comp., **12**, 29–35, 2016.

Synthetic nucleic acids can be programmed to form precise three-dimensional structures on the nanometer-scale. These thermodynamically stable complexes can serve as structural scaffolds to spatially organize functional molecules including multiple enzymes, chromophores, and force-sensing elements with internal dynamics that include substrate reaction-diffusion, excitonic energy transfer, and force-displacement response that often depend critically on both the local and global conformational dynamics of the nucleic acid assembly. We present a computational framework to compute the overdamped conformational dynamics of structured nucleic acid assemblies and apply it to a DNA-based tweezer, a nine-layer DNA origami ring, and a pointer-shaped DNA origami object, which consist of 204, 3,600, and over 7,000 basepairs, respectively.

Coarse-Grained Modeling of Nucleic Acids Using Anisotropic Gay–Berne and Electric Multipole Potentials

Guohui Li [Chinese Academy of Sciences, Dalian], Hujun Shen, Dinglin Zhang, Yan Li, and Honglei Wang

J. Chem. Theor. and Comp., **12**, 676–693, 2016.

In this work, we attempt to apply a coarse-grained (CG) model, which is based on anisotropic Gay–Berne and electric multipole (EMP) potentials, to the modeling of nucleic acids. First, a comparison has been made between the CG and atomistic models (AMBER point-charge model) in the modeling of DNA and RNA hairpin structures. The CG results have demonstrated a good quality in maintaining the nucleic acid hairpin structures, in reproducing the dynamics of backbone atoms of nucleic acids, and in describing the hydrogen-bonding interactions between nucleic acid base pairs. Second, the CG and atomistic AMBER models yield comparable results in modeling double-stranded DNA and RNA molecules.

Molecular Dynamics Simulations of 5-Hydroxycytosine Damaged DNA

Aleksandra Karolak and Arjan van der Vaart [University of South Florida]

J. Phys. Chem. B., **120**, 42–48, 2016.

Oxidation of cytosine is a leading cause of mutations and can lead to cancer. Here we report molecular dynamics simulations that characterized the structure and flexibility of 5-hydroxycytosine damaged DNA. A total of four systems were studied: undamaged DNA, damaged DNA base paired to a matching guanine, damaged DNA base paired to a mismatching adenine, and the corresponding undamaged mismatched strand.

2. METHODOLOGY

Potentials and Parameters

Coarse-grained bond and angle distributions from atomistic simulations: On the systematic parameterisation of lipid models

Samuel Genheden [University of Gothenburg]

J. Mol. Graph. and Mod., **63**, 57-64, 2016.

Coarse-grained (CG) models are popular alternatives to atomistic (AT) force fields as they enable simulations of larger systems at longer timescales. The bottom-up approach is a systematic parameterisation strategy whereby data from AT simulations are used to determine the CG parameters. This is particularly straightforward with the bond and angle parameters as a direct Boltzmann inversion can be used. Still, a reference AT force field has to be chosen. In this study, I compare three common AT force fields (Stockholm lipids, Berger and Gromos) and investigate the sampling of bond and angle distributions in two CG models (Martini and Elba).

OPLS3: A Force Field Providing Broad Coverage of Drug-like Small Molecules and Proteins

Edward Harder [Schrodinger, Inc.], Wolfgang Damm, Jon Maple, Chuanjie Wu, Mark Reboul, Jin Yu Xiang, Lingle Wang, Dmitry Lupyan, Markus K. Dahlgren, Jennifer L. Knight, Joseph W. Kaus, David S. Cerutti, Goran Krilov, William L. Jorgensen, Robert Abel, and Richard A. Friesner

J. Chem. Theor. and Comp., **12**, 281–296, 2016.

The parametrization and validation of the OPLS3 force field for small molecules and proteins are reported. Enhancements with respect to the previous version (OPLS2.1) include the addition of off-atom charge sites to represent halogen bonding and aryl nitrogen lone pairs as well as a complete refit of peptide dihedral parameters to better model the native structure of proteins. To adequately cover medicinal chemical space, OPLS3 employs over an order of magnitude more reference data and associated parameter types relative to other commonly used small molecule force fields (e.g., MMFF and OPLS_2005).

Improved Parameterization of Amine–Carboxylate and Amine–Phosphate Interactions for Molecular Dynamics Simulations Using the CHARMM and AMBER Force Fields

Jejoong Yoo and Aleksei Aksimentiev [University of Illinois at Urbana–Champaign]

J. Chem. Theor. and Comp., **12**, 430–443, 2016.

Over the past decades, molecular dynamics (MD) simulations of biomolecules have become a mainstream biophysics technique. As the length and time scales amenable to the MD method increase, shortcomings of the empirical force fields, which have been developed and validated using relatively short simulations of small molecules, become apparent. Here, we report a systematic atom pair-specific refinement of Lennard-Jones parameters (NBFIX) describing amine–carboxylate and amine–phosphate interactions, which bring MD simulations of basic peptide-mediated nucleic acid assemblies and lipid bilayer membranes into better agreement with experimental data.

Molecular Dynamics

Dynamics of Seeded A β 40-Fibril Growth from Atomistic Molecular Dynamics Simulations: Kinetic Trapping and Reduced Water Mobility in the Locking Step

Nadine Schwierz [University of California, Berkeley],
Christina V. Frost, Phillip L. Geissler, and Martin Zacharias

J. Am. Chem. Soc., **138**, 527–539, 2016.

Filamentous β -amyloid aggregates are crucial for the pathology of Alzheimer's disease. Despite the tremendous biomedical importance, the molecular pathway of growth propagation is not completely understood and remains challenging to investigate by simulations due to the long time scales involved. Here, we apply extensive all-atom molecular dynamics simulations in explicit water to obtain free energy profiles and kinetic information from position-dependent diffusion profiles for three different A β _{9–40}-growth processes: fibril elongation by single monomers at the structurally unequal filament tips and association of larger filament fragments.

Importance of long-time simulations for rare event sampling in zinc finger proteins

Ryan Godwin, William Gmeiner & Freddie R. Salsbury Jr.
[Wake Forest University]

J. Biomol. Stru. and Dyn., **34**, 125–134, 2016.

Molecular dynamics (MD) simulation methods have seen significant improvement since their inception in the late 1950s. Constraints of simulation size and duration that once impeded the field have lessened with the advent of better algorithms, faster processors, and parallel computing. . Herein, our simulations of the zinc finger NEMO (2JVX) using multiple simulations of length 15, 30, 1000, and 3000 ns are analyzed to provide clarity on this point.

Oscillatory Diffusion and Second-Order Cyclostationarity in Alanine Tripeptide from Molecular Dynamics Simulation

Ka Chun Ho and Donald Hamelberg [Georgia State University, Atlanta]

J. Chem. Theor. and Comp, **12**, 372–382, 2016.

Molecular dynamics (MD) simulation distinctly describes motions of biomolecules at high resolution and can potentially be used to explain allosteric mechanism in subcellular processes. Statistical methods are necessary to realize this potential because MD simulations generate a large volume of data and because the analysis is never efficient, objective, or thorough without using appropriate statistical approaches. Tracing the flow of information within a biomolecule requires not only a description of an overall mechanism but also a multiscale statistical description from atomic interactions to the overall mechanism.

Computationally Efficient Multiscale Reactive Molecular Dynamics to Describe Amino Acid Deprotonation in Proteins

Sangyun Lee, Ruibin Liang, Gregory A. Voth, and Jessica M. J. Swanson [University of Chicago]

J. Chem. Theor. and Comp, **12**, 879–891, 2016.

An important challenge in the simulation of biomolecular systems is a quantitative description of the protonation and deprotonation process of amino acid residues. Despite the seeming simplicity of adding or removing a positively charged hydrogen nucleus, simulating the actual protonation/deprotonation process is inherently difficult. In this article, we extend the fitting approach (called FitRMD) to create MS-RMD models for ionizable amino acids within proteins.

Molecular Dynamics (Cont'd)

Inner and Outer Coordination Shells of Mg²⁺ in CorA Selectivity Filter from Molecular Dynamics Simulations

Sunan Kitjaruwankul, Pattama Wapeesittipan, Panisak Boonamnaj, and Pornthep Sompornpisut [Chulalongkorn University]

J. Phys. Chem. B., **120**, 406–417, 2016.

Structural data of CorA Mg²⁺ channels show that the five Gly-Met-Asn (GMN) motifs at the periplasmic loop of the pentamer structure form a molecular scaffold serving as a selectivity filter. Unfortunately, knowledge about the cation selectivity of Mg²⁺ channels remains limited. Since Mg²⁺ in aqueous solution has a strong first hydration shell and apparent second hydration sphere, the coordination structure of Mg²⁺ in a CorA selectivity filter is expected to be different from that in bulk water. Hence, this study investigated the hydration structure and ligand coordination of Mg²⁺ in a selectivity filter of CorA using molecular dynamics (MD) simulations.

Molecular dynamics of water and monovalent-ions transportation mechanisms of pentameric sarcolipin

Yipeng Cao, Xue Wu, Imshik Lee [Nankai University] and Xinyu Wang

Proteins: Stru. Fun. & Bioinf., **84**, 73–81, 2016.

The Sarcolipin (SLN) is a transmembrane protein that can form a self-assembled pentamer. In this work, the homology modeling and all-atom molecular dynamic (MD) simulation was performed to study the model of SLN pentamer in POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) membrane. The potential of mean force (PMF) was calculated for transmembrane transportation of Na⁺, Cl[−] and water molecule along the pore channel of penta-SLN complex.

Visualizing global properties of a molecular dynamics trajectory

Hao Zhou [Northeastern University, Boston], Shangyang Li and Lee Makowski

Proteins: Stru. Fun. & Bioinf., **84**, 82–91, 2016.

Molecular dynamics (MD) trajectories are very large data sets that contain substantial information about the dynamic behavior of a protein. Condensing these data into a form that can provide intuitively useful understanding of the molecular behavior during the trajectory is a substantial challenge that has received relatively little attention. Here, we introduce the sigma-r plot, a plot of the standard deviation of intermolecular distances as a function of that distance. This representation of global dynamics contains within a single, one-dimensional plot, the average range of motion between pairs of atoms within a macromolecule.

QM and QM/MM

Molecular Dynamics and QM/MM Calculations Predict the Substrate-Induced Gating of Cytochrome P450 BM3 and the Regio- and Stereoselectivity of Fatty Acid Hydroxylation

Kshatresh Dutta Dubey, Binju Wang, and Sason Shaik [The Hebrew University of Jerusalem]

J. Am. Chem. Soc., **138**, 837–845, 2016.

Theory predicts herein enzymatic activity from scratch. We show that molecular dynamics (MD) simulations and quantum-mechanical/molecular mechanics (QM/MM) calculations of the fatty acid hydroxylase P450 BM3 predict the binding mechanism of the fatty acid substrate and its enantio/regioselective hydroxylation by the active species of the enzyme, Compound I. The MD simulations show that the substrate's entrance involves hydrogen-bonding interactions with Pro25, Glu43, and Leu188, which induce a huge conformational rearrangement that closes the substrate channel by pulling together the A helix and the β₁ sheet to the F/G loop.

QM and QM/MM (Cont'd)

Docking, molecular dynamics and QM/MM studies to delineate the mode of binding of CucurbitacinE to F-actin

R. Pravin Kumar, L. Roopa, Upendra Nongthomba, M.M. Sudheer Mohammed [Government Arts College, Coimbatore], Naveen Kulkarni

J. Mol.Graph. and Mod., **63**, 29-37, 2016.

CucurbitacinE (CurE) has been known to bind covalently to F-actin and inhibit depolymerization. However, the mode of binding of CurE to F-actin and the consequent changes in the F-actin dynamics have not been studied. Through quantum mechanical/molecular mechanical (QM/MM) and density function theory (DFT) simulations after the molecular dynamics (MD) simulations of the docked complex of F-actin and CurE, a detailed transition state (TS) model for the Michael reaction is proposed.

Probing the Photodynamics of Rhodopsins with Reduced Retinal Chromophores

Madushanka Manathunga, Xuchun Yang, Hoi Ling Luk, Samer Gozem, Luis Manuel Frutos, Alessio Valentini, Nicolas Ferrè, and Massimo Olivucci [Bowling Green State University]

J. Chem. Theor. and Comp., **12**, 839–850, 2016.

While the light-induced population dynamics of different photoresponsive proteins has been investigated spectroscopically, systematic computational studies have not yet been possible due to the phenomenally high cost of suitable high level quantum chemical methods and the need of propagating hundreds, if not thousands, of nonadiabatic trajectories. Here we explore the possibility of studying the photodynamics of rhodopsins by constructing and investigating quantum mechanics/molecular mechanics (QM/MM) models featuring reduced retinal chromophores.

Comparative or Homology Modeling

Rapid and enhanced remote homology detection by cascading hidden Markov model searches in sequence space

Swati Kaushik, Anu G. Nair, Eshita Mutt, Hari Prasanna Subramanian, and Ramanathan Sowdhamini [Tata Institute of Fundamental Research]

Bioinformatics. **32**, 338-344, 2016.

In the post-genomic era, automatic annotation of protein sequences using computational homology-based methods is highly desirable. However, often protein sequences diverge to an extent where detection of homology and automatic annotation transfer is not straightforward. We have developed a method to identify remote homologues more effectively from any protein sequence database by using several cascading events with Hidden Markov Models (C-HMM). We have implemented clustering of hits and profile generation of hit clusters to effectively reduce the computational timings of the cascaded sequence searches.

Ligand Docking

Attracting cavities for docking. Replacing the rough energy landscape of the protein by a smooth attracting landscape

Vincent Zoete, Thierry Schuepbach, Christophe Bovigny, Prasad Chaskar, Antoine Daina, Ute F. Röhrig and Olivier Michielin [University of Lausanne]

J. Comp. Chem., **37**, 437–447, 2016.

Molecular docking is a computational approach for predicting the most probable position of ligands in the binding sites of macromolecules and constitutes the cornerstone of structure-based computer-aided drug design. Here, we present a new algorithm called Attracting Cavities that allows molecular docking to be performed by simple energy minimizations only. The approach consists in transiently replacing the rough potential energy hypersurface of the protein by a smooth attracting potential driving the ligands into protein cavities.

Ligand Docking (Cont'd)

Inexpensive Method for Selecting Receptor Structures for Virtual Screening

Zunnan Huang [Guangdong Medical University] and Chung F. Wong

J.Chem. Infor. and Mod., **56**, 21–34, 2016.

This article introduces a screening performance index (SPI) to help select from a number of experimental structures one or a few that are more likely to identify more actives among its top hits from virtual screening of a compound library. It achieved this by docking only known actives to the experimental structures without considering a large number of decoys to reduce computational costs. The SPI is calculated by using the docking energies of the actives to all the receptor structures.

An Automated Strategy for Binding-Pose Selection and Docking Assessment in Structure-Based Drug Design

Flavio Ballante and Garland R. Marshall [Washington University School of Medicine]

J.Chem. Infor. and Mod., **56**, 54–72, 2016.

Molecular docking is a widely used technique in drug design to predict the binding pose of a candidate compound in a defined therapeutic target. Numerous docking protocols are available, each characterized by different search methods and scoring functions, thus providing variable predictive capability on a same ligand–protein system. To validate a docking protocol, it is necessary to determine a priori the ability to reproduce the experimental binding pose (i.e., by determining the docking accuracy (DA)) in order to select the most appropriate docking procedure and thus estimate the rate of success in docking novel compounds.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 63, January, 2016.

- 1-7 **In silico and in vitro screening to identify structurally diverse non-azole CYP51 inhibitors as potent antifungal agent**, Aarti Singh, Sarvesh Kumar Paliwal [Banasthali University], Mukta Sharma, Anupama Mittal, Swapnil Sharma, Jai Prakash Sharma

See Applications / Medicinal Chemistry and Drug Design.

- 8-14 **Atomistic simulation of hydrophobin HFBII conformation in aqueous and fluororous media and at the water/vacuum interface**, Giuseppina Raffaini, Roberto Milani, Fabio Ganazzoli, Giuseppe Resnati, Pierangelo Metrangolo [Politecnico di Milano]

Hydrophobins are proteins of interest for numerous applications thanks to their unique conformational and surface properties and their ability to self-assemble at interfaces. Here we report fully atomistic molecular mechanics and molecular dynamics results together with circular dichroism experimental data, aimed to study the conformational properties of the hydrophobin HFBII in a fluorinated solvent in comparison with a water solution and/or at an aqueous/vacuum interface.

- 15-21 **Cytisine basicity, solvation, log P, and log D theoretical determination as tool for bioavailability prediction**, Tomasz Pieńko [Medical University of Warsaw], Monika Grudzień, Przemysław Paweł Taciak, Aleksander Paweł Mazurek

Cytisine, an $\alpha_4\beta_2$ nicotinic receptor partial agonist, is a plant alkaloid widely used as a smoking cessation agent. Despite long history of use, knowledge on pharmacokinetics of cytisine still demands an extension. This work is aimed at theoretical determination of physicochemical parameters that affect the bioavailability of cytisine.

- 22-28 **Highly predictive support vector machine (SVM) models for anthrax toxin lethal factor (LF) inhibitors**, Xia Zhang, Elizabeth Ambrose Amin [University of Minnesota]

Anthrax is a highly lethal, acute infectious disease caused by the rod-shaped, Gram-positive bacterium *Bacillus anthracis*. In the current work, we present novel support vector machine (SVM) models with high prediction accuracy that are designed to rapidly identify potential novel, structurally diverse LF inhibitor chemical matter from compound libraries.

- 29-37 **Docking, molecular dynamics and QM/MM studies to delineate the mode of binding of CucurbitacinE to F-actin**, R. Pravin Kumar, L. Roopa, Upendra Nongthomba, M.M. Sudheer Mohammed [Government Arts College, Coimbatore], Naveen Kulkarni

See Methodology / QM and QM/MM.

- 38-48 **Prediction of binding modes and affinities of 4-substituted-2,3,5,6-tetrafluorobenzenesulfonamide inhibitors to the carbonic anhydrase receptor by docking and ONIOM calculations**, Pabitra Narayan Samanta, Kalyan Kumar Das [Jadavpur University]

See Applications / Enzyme Catalysis.

- 49-56 **An in-silico approach aimed to clarify the role of Y181C and K103N HIV-1 reverse transcriptase mutations versus Indole Aryl Sulphones**, Alberto Massarotti, Antonio Coluccia [Sapienza Università di Roma]

See Applications / Medicinal Chemistry and Drug Design.

- 57-64 **Coarse-grained bond and angle distributions from atomistic simulations: On the systematic parameterisation of lipid models**, Samuel Genheden [University of Gothenburg]

See Methodology / Potentials and Parameters.

- 65-77 **Numeric promoter description – A comparative view on concepts and general application**, Rico Beier, Dirk Labudde [University of Applied Sciences Mittweida]

Nucleic acid molecules play a key role in a variety of biological processes. Starting from storage and transfer tasks, this also comprises the triggering of biological processes, regulatory effects and the active influence gained by target binding. Based on the experimental output (in this case promoter sequences), further in silico analyses aid in gaining new insights into these processes and interactions. This study compares 26 descriptor sets obtained by applying well-known numerical description concepts to an established dataset of 38 DNA promoter sequences.

- 78-84 **Computational study of polymorphic structures of α - and β - chitin and chitosan in aqueous solution**, Roberto Ribeiro Faria, Renan Faria Guerra, Lourival Rodrigues de Sousa Neto, Luiz Frederico Motta, Eduardo de Faria Franca [Federal University of Uberlândia—UFU]

Chitin is a natural biopolymer and the second most abundant after cellulose. This polysaccharide can be found in the biomass in different polymorphic forms. Chitosan is one of the most important derivatives obtained from the deacetylation of chitin. In this work, Molecular Dynamics simulations of chitin and chitosan nanoparticles enabled us to evaluate their different conformation and solubility properties.

- 85-90 **Computational assessment of several hydrogen-free high energy compounds**, Bisheng Tan [China Academy of Engineering Physics (CAEP)], Ming Huang, Xiping Long, Jinshan Li, Guijuan Fan

Tetrazino-tetrazine-tetraoxide (TTTO) is an attractive high energy compound, but unfortunately, it is not yet experimentally synthesized so far. Isomerization of TTTO leads to its five isomers, bond-separation energies were employed to compare the global stability of six compounds, it is found that isomer 1 has the highest bond-separation energy (1204.6 kJ/mol), compared with TTTO (1151.2 kJ/mol).

- 91-98 **Inclusion complexation of pinostrobin with various cyclodextrin derivatives**, Jintawee Kicuntod, Wasinee Khuntawee, Peter Wolschann, Piamsook Pongsawasdi, Warinthorn Chavasiri, Nawee Kungwan, Thanyada Rungrotmongkol [Chulalongkorn University, Bangkok]

Pinostrobin (PNS) is one of the important flavonoids and can be abundantly found in the rhizomes of fingerroot (*Boesenbergia rotunda*) and galangal (*Alpinia galangal* and *Alpinia officinarum*), the herbal basis of Southeast Asian cooking. In the present study, molecular dynamics simulations were applied to investigate the dynamics and stability of PNS inclusion complexes with β CD and its derivatives (2,6-DM β CD, 2,6-DHP β CD, 2-HP β CD and 6-HP β CD).

- 99-109 **LOX1 inhibition with small molecules**, Chrysoula Gousiadou [Technical University of Denmark], Irene Kouskoumvekak

See Applications / Enzyme Catalysis.

- 110-124 **A systematic methodology for large scale compound screening: A case study on the discovery of novel S1PL inhibitors**, Utku Deniz, Elif Ozkirimli, Kutlu O. Ulgen [Bogazici University]

See Applications / Medicinal Chemistry and Drug Design.

- 125-133 **A MARTINI extension for Pseudomonas aeruginosa PAO1 lipopolysaccharide**, Brad Van Oosten [Brock University], Thad A. Harroun

See Applications / Membrane Proteins and Lipid peptide interactions.

Journal of Computational Chemistry, 37 (3), January, 2016.

- 321–326 **Self-consistent field for fragmented quantum mechanical model of large molecular systems**, Yingdi Jin, Neil Qiang Su, Xin Xu and Hao Hu [University of Hong Kong]

Fragment-based linear scaling quantum chemistry methods are a promising tool for the accurate simulation of chemical and biomolecular systems. Because of the coupled inter-fragment electrostatic interactions, a dual-layer iterative scheme is often employed to compute the fragment electronic structure and the total energy. To reduce the number of fragment SCF iterations and speed up the convergence of the total energy, we develop here a new SCF scheme in which the inter-fragment interactions can be updated concurrently without converging the fragment electronic structure.

- 327–335 **Glucose transformation to 5-hydroxymethylfurfural in acidic ionic liquid: A quantum mechanical study**, Arifin, Maneeporn Puripat, Daisuke Yokogawa, Vudhichai Parasuk [Chulalongkorn University] and Stephan Irle

Isomerization and transformation of glucose and fructose to 5-hydroxymethylfurfural (HMF) in both ionic liquids (ILs) and water has been studied by the reference interaction site model self-consistent field spatial electron density distribution (RISM-SCF-SEDD) method coupled with ab initio electronic structure theory, namely coupled cluster single, double, and perturbative triple excitation (CCSD(T)).

- 336–344 **DOX: A new computational protocol for accurate prediction of the protein–ligand binding structures**, Li Rao, Bo Chi, Yanliang Ren, Yongjian Li, Xin Xu and Jian Wan [Central China Normal University, Wuhan]

See Applications / Membrane Proteins and Lipid peptide interactions.

- 345–353 **Assessment of the extended Koopmans' theorem for the chemical reactivity: Accurate computations of chemical potentials, chemical hardnesses, and electrophilicity indices**, Dilan Yildiz and Uğur Bozkaya [Atatürk University, Erzurum]

The extended Koopmans' theorem (EKT) provides a straightforward way to compute ionization potentials and electron affinities from any level of theory. Although it is widely applied to ionization potentials, the EKT approach has not been applied to evaluation of the chemical reactivity. We present the first benchmarking study to investigate the performance of the EKT methods for predictions of chemical potentials (μ) (hence electronegativities), chemical hardnesses (η), and electrophilicity indices (ω).

- 354–365 **Revision of the GROMOS 56A6_{CARBO} force field: Improving the description of ring-conformational equilibria in hexopyranose-based carbohydrates chains**, Wojciech Plazinski, Alice Lonardi and Philippe H. Hünenberger [ETH Hönggerberg, HCI]

This article describes a revised version 56A6_{CARBO_R} of the GROMOS 56A6_{CARBO} force field for hexopyranose-based carbohydrates. The simulated properties of unfunctionalized hexopyranoses are unaltered with respect to 56A6_{CARBO}.

- 366–377 **Buckybowls as adsorbents for CO₂, CH₄, and C₂H₂: Binding and structural insights from computational study**, M. Althaf Hussain, Dolly Vijay and G. Narahari Sastry [CSIR-Indian Institute of Chemical Technology]

Noncovalent functionalization of buckybowls sumanene (S), corannulene (R), and coronene (C) with greenhouse gases (GGs) such as CO₂, CH₄ (M), and C₂H₂ (A) has been studied using hybrid density functional theory.

Journal of Computational Chemistry, 37 (4), February, 2016.

- 395–403 **Spin-orbit ZORA and four-component Dirac–Coulomb estimation of relativistic corrections to isotropic nuclear shieldings and chemical shifts of noble gas dimers**, Marzena Jankowska, Teobald Kupka [University of Copenhagen], Leszek Stobiński, Rasmus Faber, Evanildo G. Lacerda Jr. and Stephan P. A. Sauer

Hartree–Fock and density functional theory with the hybrid B3LYP and general gradient KT2 exchange–correlation functionals were used for nonrelativistic and relativistic nuclear magnetic shielding calculations of helium, neon, argon, krypton, and xenon dimers and free atoms.

- 404–415 **Protein:Ligand binding free energies: A stringent test for computational protein design**, Karen Druart, Zoltan Palmai, Eyaz Omarjee and Thomas Simonson [Ecole Polytechnique, Palaiseau]

See Applications / Membrane Proteins and Lipid peptide interactions.

- 416–425 **DIRECT-ID: An automated method to identify and quantify conformational variations—application to β_2 -adrenergic GPCR**, Sirish Kaushik Lakkaraju, Justin A. Lemkul, Jing Huang and Alexander D. MacKerell Jr. [University of Maryland Baltimore]

See Applications / Protein Conformational Analysis.

- 426–436 **Protein folds recognized by an intelligent predictor based-on evolutionary and structural information**, Ngaam J. Cheung, Xue-Ming Ding and Hong-Bin Shen [Shanghai Jiao Tong University]

See Applications / Protein Folding.

- 437–447 **Attracting cavities for docking. Replacing the rough energy landscape of the protein by a smooth attracting landscape**, Vincent Zoete, Thierry Schuepbach, Christophe Bovigny, Prasad Chaskar, Antoine Daina, Ute F. Röhrig and Olivier Michielin [University of Lausanne]

See Methodology / Ligand Docking.

- 448–459 **Shift-and-invert parallel spectral transformation eigensolver: Massively parallel performance for density-functional based tight-binding**, Murat Keçeli, Hong Zhang, Peter Zapol, David A. Dixon and Albert F. Wagner [Argonne National Laboratory]

The Shift-and-invert parallel spectral transformations (SIPs), a computational approach to solve sparse eigenvalue problems, is developed for massively parallel architectures with exceptional parallel scalability and robustness.

Journal of Computational Chemistry, 37 (5), February, 2016.

- 467–476 **Diffusive dynamics of DNA unzipping in a nanopore**, Anna Stachiewicz [Adam Mickiewicz University] and Andrzej Molski

See Applications / Protein-Nucleic acids.

- 477–486 **Cost and sensitivity of restricted active-space calculations of metal L-edge X-ray absorption spectra**, Rahul V. Pinjari, Mickaël G. Delcey, Meiyuan Guo, Michael Odelius and Marcus Lundberg [Uppsala University, Uppsala]

The restricted active-space (RAS) approach can accurately simulate metal L-edge X-ray absorption spectra of first-row transition metal complexes without the use of any fitting parameters. These characteristics provide a unique capability to identify unknown chemical species and to analyze their electronic structure. To find the best balance between cost and accuracy, the sensitivity of the simulated spectra with respect to the method variables has been tested for two models, $[\text{FeCl}_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{3-}$.

- 487–493 **Nontotally symmetric trifurcation of an $\text{S}_{\text{N}}2$ reaction pathway**, Yu Harabuchi, Yuriko Ono, Satoshi Maeda, Tetsuya Taketsugu, Kristopher Keipert and Mark S. Gordon [Iowa State University, Ames]

A new type of reaction pathway which involves a nontotally symmetric trifurcation was found and investigated for a typical $\text{S}_{\text{N}}2$ -type reaction, $\text{NC}^- + \text{CH}_3\text{X} \rightarrow \text{NC}-\text{CH}_3 + \text{X}^-$ ($\text{X} = \text{F}, \text{Cl}$). A nontotally symmetric valley-ridge inflection (VRI) point was located along the C_{3v} reaction path.

- 494–506 **Scalable improvement of SPME multipolar electrostatics in anisotropic polarizable molecular mechanics using a general short-range penetration correction up to quadrupoles**, Christophe Narth,

Louis Lagardère, Étienne Polack, Nohad Gresh, Qiantao Wang, David R. Bell, Joshua A. Rackers, Jay W. Ponder, Pengyu Y. Ren [Laboratoire de Chimie Théorique] and Jean-Philip Piquemal

We propose a general coupling of the Smooth Particle Mesh Ewald SPME approach for distributed multipoles to a short-range charge penetration correction modifying the charge-charge, charge-dipole and charge-quadrupole energies. Such an approach significantly improves electrostatics when compared to ab initio values and has been calibrated on Symmetry-Adapted Perturbation Theory reference data.

Journal of Molecular Modeling, 22 (2), February, 2016.

- 51 **A two-layer ONIOM study of thiophene cracking catalyzed by proton- and cation-exchanged FAU zeolite,** Yingxin Sun, Xinfeng Mao, Supeng Pei [Shanghai Institute of Technology]

A two-layer ONIOM study on the hydrodesulfurization mechanism of thiophene in H-FAU and M-FAU ($M = \text{Li}^+$, Na^+ , and K^+) has been carried out. The calculated results reveal that in H-FAU, for a unimolecular mechanism, the rate-determining step is hydrogenation of alkoxide intermediate. The assistance of H_2O and H_2S molecules does not reduce the difficulty of the C-S bond cracking step more effectively.

- 50 **The encapsulated lithium effect on the first hyperpolarizability of C_{60}Cl_2 and C_{60}F_2 ,** Yao-Dong Song [Fujian University of Technology], Liang Wang, Li-Ming Wu, Qiao-Ling Chen, Fa-Kun Liu, Xiao-Wen Tang

In this paper, we report a study on the structure and first hyperpolarizability of C_{60}Cl_2 and C_{60}F_2 . The calculation results show that the first hyperpolarizabilities of C_{60}Cl_2 and C_{60}F_2 were 172 au and 249 au, respectively.

- 49 **A fast loop-closure algorithm to accelerate residue matching in computational enzyme design,** Jing Xue, Xiaoqiang Huang, Min Lin, Yushan Zhu [Tsinghua University]

See Applications / Enzyme Catalysis.

- 48 **Metal-metal bonding and aromaticity in $[\text{M}_2(\text{NHCHNH})_3]_2(\mu\text{-E})_2$ ($\text{E} = \text{O}, \text{S}$; $\text{M} = \text{Nb}, \text{Mo}, \text{Tc}, \text{Ru}, \text{Rh}$),** Xiuli Yan, Lingpeng Meng, Zheng Sun, Xiaoyan Li [Hebei Normal University]

The nature of M-M bonding and aromaticity of $[\text{M}_2(\text{NHCHNH})_3]_2(\mu\text{-E})_2$ ($\text{E} = \text{O}, \text{S}$; $\text{M} = \text{Nb}, \text{Mo}, \text{Tc}, \text{Ru}, \text{Rh}$) was investigated using atoms in molecules (AIM) theory, electron localization function (ELF), natural bond orbital (NBO) and molecular orbital analysis.

- 47 **COMPASS II: extended coverage for polymer and drug-like molecule databases,** Huai Sun [Shanghai Jiao Tong University], Zhao Jin, Chunwei Yang, Reinier L. C. Akkermans, Struan H. Robertson, Neil A. Spenley, Simon Miller, Stephen M. Todd

The COMPASS II force field has been developed by extending the coverage of the COMPASS force field (J Phys Chem B 102(38):7338–7364, 1998) to polymer and drug-like molecules found in popular databases. Using a fragmentation method to systematically construct small molecules that exhibit key functional groups found in these databases, parameters applicable to database compounds were efficiently obtained.

- 46 **The mechanism of the effect of U18666a on blocking the activity of 3 β -hydroxysterol Δ -24-reductase (DHCR24): molecular dynamics simulation study and free energy analysis**, Xiaoping Quan, Xiuqiang Chen, Deliang Sun, Bo Xu, Linlin Zhao, Xiaoqian Shi, Hongsheng Liu, Bing Gao, Xiuli Lu [Liaoning University]

See Applications / Enzyme Catalysis.

- 45 **Electronic structure, rovibrational, and dipole moment calculations for the AsCl molecule**, Khaled A. Mourad, Saleh N. Abdulal, Mahmoud Korek [Beirut Arab University]

The potential energy curves of the 19 lowest-lying singlet and triplet electronic states in the $^{2S+1}\Lambda^{(+/-)}$ representation of the AsCl molecule have been investigated using the complete active space self-consistent field (CASSCF) with multireference configuration interaction (MRCI+Q) method including single and double excitations and with the Davidson correction.

- 44 **Theoretical study of enzymatically catalyzed tautomerization of carbon acids in aqueous solution: quantum calculations and steered molecular dynamics simulations**, Santiago Tolosa [Universidad de Extremadura], Antonio Hidalgo, Jorge A. Sansón

The thermodynamics and kinetics of enzymatically assisted reactions of carbon acids were studied theoretically in this work. Quantum electronic (QE) structure calculations and steered molecular dynamics (SMD) simulations were carried out.

- 43 **Research on structures, mechanical properties, and mechanical responses of TKX-50 and TKX-50 based PBX with molecular dynamics**, Song Ma, Yajin Li, Yang Li, Yunjun Luo [Beijing Institute of Technology]

To improve the practicality and safety of a novel explosive dihydroxylamm onium 5,5'-bis (tetrazole)-1,1'-diolate (TKX-50), polyvinylidene difluoride (PVDF) and polychlorotrifluoroethylene (PCTFE) were respectively added to the TKX-50, forming the polymer-bonded explosives (PBX). Interfacial and mechanical properties of PBX were investigated through molecular dynamics (MD) method, desensitizing mechanisms of fluorine-polymers for TKX-50 were researched by compression and bulk shear simulations.

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About 95 Papers from more than 30 Journals are cited.

1 APPLICATIONS (70) Page 2

1.1 Small Molecules (9)

Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 4

1.2 Biopolymers (61)

Bioinformatics and Cheminformatics	Page 5	Enzyme Catalysis	Page 12
Protein Conformational Analysis	Page 5	Protein-Protein Interactions	Page 15
Protein Structure Analysis	Page 7	Membrane Proteins	Page 16
Protein Dynamics	Page 8	Protein Folding	Page 18
Free Energy Calculations	Page 10	Protein-Nucleic Acids	Page 19
Ligand Binding	Page 10	Nucleic Acids	Page 20

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (11) Page 21

QSAR	Page 21	Free Energy Perturbation	Page 22
Potentials and Parameters	Page 21	QM & QM/MM Modeling	Page 23
Molecular Dynamics	Page 22	Ligand Docking	Page 24

3 JOURNAL REVIEWS (5) Page 25

Journal of Molecular Graphics and Modeling, 64, March, 2016.
 Journal of Computational Chemistry, 37 (6), March, 2016.
 Journal of Computational Chemistry, 37 (7), March, 2016.
 Journal of Computational Chemistry, 37 (8), March, 2016.
 Journal of Molecular Modeling, 22 (3), March, 2016.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 34

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

PDID: database of molecular-level putative protein–drug interactions in the structural human proteome

Chen Wang, Gang Hu, Kui Wang, Michal Brylinski, Lei Xie, and Lukasz Kurgan [University of Alberta, Edmonton]

Bioinformatics. **32**, 579-586, 2016.

Many drugs interact with numerous proteins besides their intended therapeutic targets and a substantial portion of these interactions is yet to be elucidated. Protein–Drug Interaction Database (PDID) addresses incompleteness of these data by providing access to putative protein–drug interactions that cover the entire structural human proteome. PDID covers 9652 structures from 3746 proteins and houses 16 800 putative interactions generated from close to 1.1 million accurate, all-atom structure-based predictions for several dozens of popular drugs.

Molecular docking based virtual screening of natural compounds as potential BACE1 inhibitors: 3D QSAR pharmacophore mapping and molecular dynamics analysis

Akhil Kumar, Sudeep Roy, Shubhandra Tripathi & Ashok Sharma [CSIR-Central Institute of Medicinal and Aromatic Plants]

J. Biomol. Stru. and Dyn., **34**, 239-249, 2016.

Beta-site APP cleaving enzyme1 (BACE1) catalyzes the rate determining step in the generation of A β peptide and is widely considered as a potential therapeutic drug target for Alzheimer's disease (AD). Active site of BACE1 contains catalytic aspartic (Asp) dyad and flap. Asp dyad cleaves the substrate amyloid precursor protein with the help of flap. Currently, there are no marketed drugs available against BACE1 and existing inhibitors are mostly pseudopeptide or synthetic derivatives. This study screens the natural database InterBioScreen, followed by three-dimensional (3D) QSAR pharmacophore modeling, mapping, in silico ADME/T predictions to find the potential BACE1 inhibitors.



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Medicinal Chemistry and Drug Design (Cont'd)

Design and synthesis of a novel class of carbonic anhydrase-IX inhibitor 1-(3-(phenyl/4-fluorophenyl)-7-imino-3H-[1,2,3]triazolo[4,5d]pyrimidin 6(7H)yl)urea

Shikha Kumari, Danish Idrees, Chandra Bhushan Mishra, Amresh Prakash, Wahiduzzaman, Faizan Ahmad, Md. Imtaiyaz Hassan, Manisha Tiwari [University of Delhi]

J. Mol.Graph. and Mod., **64**, 101-109 , 2016.

Carbonic anhydrase IX (CAIX) is a promising target in cancer therapy especially in the case of hypoxia-induced tumors. The selective inhibition of CA isozymes is a challenging task in drug design and discovery process. Here, we performed fluorescence-binding studies and inhibition assay combined with molecular docking and molecular dynamics (MD) simulation analyses to determine the binding affinity of two synthesized triazolo-pyrimidine urea derived (TPUI and TPUII) compounds with CAIX and CAII.

Insights into the Inhibitory Mechanism of D13-9001 to the Multidrug Transporter AcrB through Molecular Dynamics Simulations

Zhicheng Zuo, Jingwei Weng, and Wenning Wang [Fudan University, Shanghai]

J. Phys. Chem. B., **120**, 2145–2154, 2016.

The resistance-nodulation-cell division transporter AcrB is responsible for energy transduction and substrate recognition in the tripartite AcrAB-TolC efflux system in *Escherichia coli*. Despite a broad substrate specificity, only a few compounds have been cocrystallized with AcrB inside the distal binding pocket (DBP), including doxorubicin (DOX) and D13-9001. D13-9001 is a promising efflux pump inhibitor that potentiates the efficacy of a wide variety of antibiotics. To understand its inhibition effect under the framework of functional rotating mechanism, we performed targeted and steered molecular dynamics simulations to compare the binding and extrusion processes of this inhibitor and the substrate DOX in AcrB.

Insights into regioselective metabolism of mefenamic acid by cytochrome P450 BM3 mutants through crystallography, docking, molecular dynamics, and free energy calculations

Luigi Capoferri, Rasmus Leth, Ernst ter Haar, Arun K. Mohanty, Peter D. J. Grootenhuis, Eduardo Vottero, Jan N. M. Commandeur, Nico P. E. Vermeulen, Flemming Steen Jørgensen, Lars Olsen and Daan P. Geerke [VU University]

Proteins: Stru. Fun. & Bioinf., **84**, 383–396, 2016.

Cytochrome P450 BM3 (CYP102A1) mutant M11 is able to metabolize a wide range of drugs and drug-like compounds. Among these, M11 was recently found to be able to catalyze formation of human metabolites of mefenamic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs). Interestingly, single active-site mutations such as V87I were reported to invert regioselectivity in NSAID hydroxylation. In this work, we combine crystallography and molecular simulation to study the effect of single mutations on binding and regioselective metabolism of mefenamic acid by M11 mutants.

Exploring the unbinding of Leishmania (L.) amazonensis CPB derived-epitopes from H2 MHC class I proteins

Artur M. L. Brandt, Paulo Ricardo Batista, Franklin Souza-Silva, Carlos Roberto Alves [Instituto Oswaldo Cruz] and Ernesto Raul Caffarena

Proteins: Stru. Fun. & Bioinf., **84**, 473–487, 2016.

New strategies to control Leishmania disease demand an extensive knowledge about several aspects of infection including the understanding of its molecular events. In murine models, cysteine proteinase B from *Leishmania amazonensis* promotes regulation of immune response, and fragments from its C-terminus extension (cyspep) can play a decisive role in the host-parasite interaction. The interaction between cyspep-derived peptides and major histocompatibility complex (MHC) proteins is a crucial factor in Leishmania infections. Seven cyspep-derived peptides, previously identified as capable of interacting with H-2 (murine) MHC class I proteins, were studied in this work.

Carbon Nanoparticles

Molecular dynamics simulation of non-covalent single-walled carbon nanotube functionalization with surfactant peptides

Abolfazl Barzegar [University of Tabriz], Alireza Mansouri, Jafar Azamat

J. Mol.Graph. and Mod., **64**, 75-84, 2016.

Non-covalent functionalized single-walled carbon nanotubes (SWCNTs) with improved solubility and biocompatibility can successfully transfer drugs, DNA, RNA, and proteins into the target cells. Theoretical studies such as molecular docking and molecular dynamics simulations in fully atomistic scale were used to investigate the hydrophobic and aromatic π - π -stacking interaction of designing four novel surfactant peptides for non-covalent functionalization of SWCNTs. The results indicated that the designed peptides have binding affinity towards SWCNT with constant interactions during MD simulation times, and it can even be improved by increasing the number of tryptophan residues.

Dynamic mechanical characterization of CNT-PP nanocomposites

A. Mandal [Indian Institute of Technology Delhi], S. P. Singh, R. Prasad

J. Mol.Mod., **22**, 66, 2016.

In this study, molecular dynamic simulations were used to carry out a dynamic mechanical analysis of polymer nanocomposites (PNC) containing polypropylene (PP) and various volume fractions of single walled carbon nanotubes (SWCNTs). After assembling the composite unit cell, relaxation studies were performed by loading the specimen to a predetermined strain under quasistatic loading and then sustaining the strain while allowing the material to relax. Nano level readjustments of the polymer chains took place during this process, reducing the overall stress levels in the specimen.

On the vibrational behavior of single- and double-walled carbon nanotubes under the physical adsorption of biomolecules in the aqueous environment: a molecular dynamics study

S. Ajori [University of Guilan], R. Ansari, M. Darvizeh

J. Mol.Mod., **22**, 62, 2016.

The adsorption of biomolecules on the walls of carbon nanotubes (CNTs) in an aqueous environment is of great importance in the field of nanobiotechnology. In this study, molecular dynamics (MD) simulations were performed to understand the mechanical vibrational behavior of single- and double-walled carbon nanotubes (SWCNTs and DWCNTs) under the physical adsorption of four important biomolecules (L-alanine, guanine, thymine, and uracil) in vacuum and an aqueous environment.

1.2. Biopolymers

Bioinformatics and Cheminformatics

IsoMIF Finder: online detection of binding site molecular interaction field similarities

Matthieu Chartier, Etienne Adriansen, and Rafael Najmanovich [University of Sherbrooke]

Bioinformatics. **32**, 621-623, 2016.

IsoMIF Finder is an online server for the identification of molecular interaction field (MIF) similarities. User defined binding site MIFs can be compared to datasets of pre-calculated MIFs or against a user-defined list of PDB entries. The interface can be used for the prediction of function, identification of potential cross-reactivity or polypharmacological targets and drug repurposing. Detected similarities can be viewed in a browser or within a PyMOL session.

Flexible CDOCKER: Development and application of a pseudo-explicit structure-based docking method within CHARMM

Jessica K. Gagnon, Sean M. Law and Charles L. Brooks III [University of Michigan, Ann Arbor]

J. Comp. Chem., **37**, 753–762, 2016.

Protein-ligand docking is a commonly used method for lead identification and refinement. While traditional structure-based docking methods represent the receptor as a rigid body, recent developments have been moving toward the inclusion of protein flexibility. Proteins exist in an interconverting ensemble of conformational states, but effectively and efficiently searching the conformational space available to both the receptor and ligand remains a well-appreciated computational challenge. To this end, we have developed the Flexible CDOCKER method as an extension of the family of complete docking solutions available within CHARMM.

Protein Conformational Analysis

Computational analysis of spiro-oxindole inhibitors of the MDM2-p53 interaction: insights and selection of novel inhibitors

Wei Huang, Lulu Cai, Can Chen, Xin Xie, Qiong Zhao, Xing Zhao, Hong-yun Zhou, Bo Han [Chengdu University of Traditional Chinese Medicine] & Cheng Peng

J. Biomol. Stru. and Dyn., **34**, 341-351, 2016.

Since MDM2 is an inhibitor of the p53 tumor suppressor, disrupting the MDM2-p53 interaction is a promising approach for cancer therapy. Here, we used molecular dynamics simulations followed by free energy decomposition analysis to study conformational changes in MDM2 induced by three known spiro-oxindole inhibitors. Analysis of individual energy terms suggests that van der Waals and electrostatic interactions explain much of the binding affinities of these inhibitors. Binding free energies calculated for the three inhibitors using the molecular mechanics-generalized Born surface area model were consistent with experimental data, suggesting the validity of this approach.

Protein Conformational Analysis (Cont'd)

Multiscale enhanced sampling of intrinsically disordered protein conformations

Kuo Hao Lee and Jianhan Chen [Kansas State University]

J. Comp. Chem., **37**, 550–557, 2016.

In a recently developed multiscale enhanced sampling (MSES) technique, topology-based coarse-grained (CG) models are coupled to atomistic force fields to enhance the sampling of atomistic protein conformations. Here, the MSES protocol is refined by designing more sophisticated Hamiltonian/temperature replica exchange schemes that involve additional parameters in the MSES coupling restraint potential, to more carefully control how conformations are coupled between the atomistic and CG models.

Self-guided Langevin dynamics via generalized Langevin equation

Xiongwu Wu [National Institutes of Health (NIH), Bethesda], Bernard R. Brooks and Eric Vanden-Eijnden

J. Comp. Chem., **37**, 595–601, 2016.

Self-guided Langevin dynamics (SGLD) is a molecular simulation method that enhances conformational search and sampling via acceleration of the low frequency motions of the system. This acceleration is produced via introduction of a guiding force which breaks down the detailed-balance property of the dynamics, implying that some reweighting is necessary to perform equilibrium sampling. Here, we eliminate the need of reweighting and show that the NVT and NPT ensembles are sampled exactly by a new version of self-guided motion involving a generalized Langevin equation (GLE) in which the random force is modified so as to restore detailed-balance.

Demonstrating an Order-of-Magnitude Sampling Enhancement in Molecular Dynamics Simulations of Complex Protein Systems

Albert C. Pan, Thomas M. Weinreich, Stefano Piana, and David E. Shaw [D. E. Shaw Research, New York]

J. Chem. Theor. and Comp, **12**, 1360–1367, 2016.

Molecular dynamics (MD) simulations can describe protein motions in atomic detail, but transitions between protein conformational states sometimes take place on time scales that are infeasible or very expensive to reach by direct simulation. Enhanced sampling methods, the aim of which is to increase the sampling efficiency of MD simulations, have thus been extensively employed. Here, we obtain sufficiently converged simulations of three proteins to evaluate the performance of simulated tempering, a member of a widely used class of enhanced sampling methods that use elevated temperature to accelerate sampling.

Using Local States To Drive the Sampling of Global Conformations in Proteins

Alessandro Pandini and Arianna Fornili [Queen Mary University of London]

J. Chem. Theor. and Comp, **12**, 1368–1379, 2016.

Conformational changes associated with protein function often occur beyond the time scale currently accessible to unbiased molecular dynamics (MD) simulations, so that different approaches have been developed to accelerate their sampling. Here we investigate how the knowledge of backbone conformations preferentially adopted by protein fragments, as contained in precalculated libraries known as structural alphabets (SA), can be used to explore the landscape of protein conformations in MD simulations.

Protein Conformational Analysis (Cont'd)

Disagreement Between the Structure of the dTpT Thymine Pair Determined by NMR and Molecular Dynamics Simulations Using Amber 14 Force Fields

Collins Nganou, Scott D. Kennedy, and David W. McCamant
[University of Rochester, Rochester]

J. Phys. Chem. B., **120**, 1250–1258, 2016.

We report a disagreement between the predicted structures of the dTpT thymine pair (thymidylyl(3' → 5')thymidine) using nuclear magnetic resonance (NMR) spectroscopy and molecular dynamics (MD) simulations using the AMBER ff14SB and ff14 + ϵ/ζ OL1 + χ OL4 force fields for DNA. The NMR structure was determined using NOE couplings to thymine's H6 and J_{HH} couplings between sugar protons. The MD simulation used replica exchange methods to produce converged statistics in a 500 ns trajectory.

Comparison of Replica Exchange Simulations of a Kinetically Trapped Protein Conformational State and its Native Form

Mark A. Olson [USAMRIID, Frederick], Patricia M. Legler, and Ellen R. Goldman

J. Phys. Chem. B., **120**, 2234–2240, 2016.

Recently an X-ray crystallographic structure of a single-domain antibody was reported with the protein chain trapped in a rare homodimeric form. One of the conformers appears to exhibit a misfolded region, and thus presumably the configurational stability is less favorable. To investigate whether simulation methods can detect any difference between the conformers and buttress the notion that one conformation is trapped on a pathway that incurs lower activation energy to unfold, adaptive temperature-based replica exchange simulations were applied to each chain to model conformational transitions.

General trends of dihedral conformational transitions in a globular protein

Yinglong Miao [University of California at San Diego], Jerome Baudry, Jeremy C. Smith and J. Andrew McCammon

Proteins: Stru. Fun. & Bioinf., **84**, 501–514, 2016.

Dihedral conformational transitions are analyzed systematically in a model globular protein, cytochrome P450cam, to examine their structural and chemical dependences through combined conventional molecular dynamics (cMD), accelerated molecular dynamics (aMD) and adaptive biasing force (ABF) simulations. The aMD simulations are performed at two acceleration levels, using dihedral and dual boost, respectively. In comparison with cMD, aMD samples protein dihedral transitions approximately two times faster on average using dihedral boost, and ~3.5 times faster using dual boost.

Protein Structure Analysis

Fit3D: a web application for highly accurate screening of spatial residue patterns in protein structure data

Florian Kaiser [University of Applied Sciences Mittweida], Alexander Eisold, Sebastian Bittrich, and Dirk Labudde

Bioinformatics. **32**, 792–794, 2016.

The clarification of linkage between protein structure and function is still a demanding process and can be supported by comparison of spatial residue patterns, so-called structural motifs. However, versatile up-to-date resources to search for local structure similarities are rare. We present Fit3D, an easily accessible web application for highly accurate screening of structural motifs in 3D protein data.

Protein Structure Analysis (Cont'd)

Characterization of the Free State Ensemble of the CoRNR Box Motif by Molecular Dynamics Simulations

Elio A. Cino [The University of Western Ontario], Wing-Yiu Choy, and Mikko Karttunen

J. Phys. Chem. B., **120**, 1060–1068, 2016.

Intrinsically disordered proteins (IDPs) and regions are highly prevalent in eukaryotic proteomes, and like folded proteins, they perform essential biological functions. Structural data is crucial for understanding the molecular basis of protein interactions and development of targeted pharmaceuticals, but IDPs present considerable challenges to experimental techniques. Here, the free state ensemble of the nuclear receptor corepressor 1 (NCOR1) CoRNR box 3 motif, which is important for binding to nuclear receptors to control gene expression, is studied using MD simulations of a total of 8 μ s.

Protein-fold recognition using an improved single-source K diverse shortest paths algorithm

John Lhota and Lei Xie [Hunter College]

Proteins: Stru. Fun. & Bioinf., **84**, 467–472, 2016.

Protein structure prediction, when construed as a fold recognition problem, is one of the most important applications of similarity search in bioinformatics. A new protein-fold recognition method is reported which combines a single-source K diverse shortest path (SSKDSP) algorithm with Enrichment of Network Topological Similarity (ENTS) algorithm to search a graphic feature space generated using sequence similarity and structural similarity metrics. A modified, more efficient SSKDSP algorithm is developed to improve the performance of graph searching.

Protein Dynamics

Dissociation of a Dynamic Protein Complex Studied by All-Atom Molecular Simulations

Liqun Zhang, Susmita Borthakur, Matthias Buck [Case Western Reserve University]

Biophysical Journal., **110**, 877-886, 2016.

The process of protein complex dissociation remains to be understood at the atomic level of detail. Computers now allow microsecond timescale molecular-dynamics simulations, which make the visualization of such processes possible. Here, we investigated the dissociation process of the EphA2-SHIP2 SAM-SAM domain heterodimer complex using unrestrained all-atom molecular-dynamics simulations. Previous studies on this system have shown that alternate configurations are sampled, that their interconversion can be fast, and that the complex is dynamic by nature.

Proton Transfer and Structure-Specific Fluorescence in Hydrogen Bond-Rich Protein Structures

Dorothea Pinotsi, Luca Grisanti, Pierre Mahou, Ralph Gebauer, Clemens F. Kaminski, Ali Hassanali, and Gabriele S. Kaminski Schierle [University of Cambridge, Pembroke Street]

J. Am. Chem. Soc., **138**, 3046–3057, 2016.

Protein structures which form fibrils have recently been shown to absorb light at energies in the near UV range and to exhibit a structure-specific fluorescence in the visible range even in the absence of aromatic amino acids. However, the molecular origin of this phenomenon has so far remained elusive. Here, we combine ab initio MD simulations and fluorescence spectroscopy to demonstrate that these intrinsically fluorescent protein fibrils are permissive to proton transfer across hydrogen bonds which can lower electron excitation energies and thereby decrease the likelihood of energy dissipation associated with conventional hydrogen bonds.

Protein Dynamics (Cont'd)

The role of the acidic domain of α -synuclein in amyloid fibril formation: a molecular dynamics study

SeongByeong Park, Jeseong Yoon, Soonmin Jang, Kyunghee Lee & Seokmin Shin [Seoul National University]

J. Biomol. Stru. and Dyn., **34**, 376-383, 2016.

The detailed mechanism of the pathology of α -synuclein in the Parkinson's disease has not been clearly elucidated. Recent studies suggested a possible chaperone-like role of the acidic C-terminal region of α -synuclein in the formation of amyloid fibrils. It was also previously demonstrated that the α -synuclein amyloid fibril formation is accelerated by mutations of proline residues to alanine in the acidic region. We performed replica exchange molecular dynamics simulations of the acidic and nonamyloid component (NAC) domains of the wild type and proline-to-alanine mutants of α -synuclein under various conditions.

Coupled folding and binding with 2D Window-Exchange Umbrella Sampling

Alex Dickson, Logan S. Ahlstrom and Charles L. Brooks III [The University of Michigan, Ann Arbor]

J. Comp. Chem., **37**, 587–594, 2016.

Intrinsically disordered regions of proteins can gain structure by binding to a partner. Structure-based models have proven themselves capable of revealing fundamental aspects of how CFaB occurs, however, typical methods to enhance the sampling of these transitions, such as replica exchange, do not adequately sample the transition state region of this extremely rare process. Here, we use a variant of Umbrella Sampling to enforce sampling of the transition states of CFaB of HdeA monomers at neutral pH, an extremely rare process that occurs over timescales ranging from seconds to hours.

A highly efficient hybrid method for calculating the hydration free energy of a protein

Hiraku Oshima and Masahiro Kinoshita [Kyoto University, Uji]

J. Comp. Chem., **37**, 712–723, 2016.

We develop a new method for calculating the hydration free energy (HFE) of a protein with any net charge. The polar part of the energetic component in the HFE is expressed as a linear combination of four geometric measures (GMs) of the protein structure and the generalized Born (GB) energy plus a constant. The other constituents in the HFE are expressed as linear combinations of the four GMs. The coefficients (including the constant) in the linear combinations are determined using the three-dimensional reference interaction site model (3D-RISM) theory applied to sufficiently many protein structures.

Contribution of main chain and side chain atoms and their locations to the stability of thermophilic proteins

Dharma Rao Tompa, M.Michael Gromiha, K. Saraboji [SASTRA University, Thanjavur]

J. Mol.Graph. and Mod., **64**, 85-93, 2016.

Proteins belonging to the same class, having similar structures thus performing the same function are known to have different thermal stabilities depending on the source— thermophile or mesophile. The variation in thermo-stability has not been attributed to any unified factor yet and understanding this phenomenon is critically needed in several areas, particularly in protein engineering to design stable variants of the proteins. Toward this motive, the present study focuses on the sequence and structural investigation of a dataset of 373 pairs of proteins.

Free Energy Calculations

Free energy simulations with the AMOEBA polarizable force field and metadynamics on GPU platform

Xiangda Peng, Yuebin Zhang, Huiying Chu and Guohui Li
[Chinese Academy of Sciences, Dalian]

J. Comp. Chem., **37**, 614–622, 2016.

The free energy calculation library PLUMED has been incorporated into the OpenMM simulation toolkit, with the purpose to perform enhanced sampling MD simulations using the AMOEBA polarizable force field on GPU platform. Two examples, (I) the free energy profile of water pair separation (II) alanine dipeptide dihedral angle free energy surface in explicit solvent, are provided here to demonstrate the accuracy and efficiency of our implementation. The converged free energy profiles could be obtained within an affordable MD simulation time when the AMOEBA polarizable force field is employed.

Ligand Binding/Docking

Computational studies of pandemic 1918 and 2009 H1N1 hemagglutinins bound to avian and human receptor analogs

S. Kannan & P. Kolandaivel [Bharathiar University, Coimbatore]

J. Biomol. Stru. and Dyn., **34**, 272–289, 2016.

The purpose of this work was to study the binding properties of two pandemic influenza A virus 1918 H1N1 (SC1918) and 2009 H1N1 (CA09) hemagglutinin (HA) with avian and human receptors. The quantum chemical calculations have been performed to analyze the interactions of 130 loop, 190 helix, 220 loop region, and conserved residues 95,145,153–155, of pandemic viruses' HA with sialo-trisaccharide receptor of avian and human using density functional theory. The HA's residues Tyr 95, Ala 138, Gln 191, Arg 220, and Asp 225 from the above regions have stronger interaction with avian receptor.

The binding mechanism of a novel nicotinamide isostere inhibiting with TNKSs: a molecular dynamic simulation and binding free energy calculation

Ting-Ting Feng, Yan-Jun Zhang, H. Chen, Song Fan & Ju-Guang Han [The First Affiliated Hospital of Anhui Medical University]

J. Biomol. Stru. and Dyn., **34**, 517–528, 2016.

Tankyrases (TNKSs), a member of human poly (ADP-ribose) polymerase (PARP) protein superfamily, plays a key role in regulation of cell proliferation. Among the representative proteins of the PARPs family, it is found that the inhibitors have high selectivity for Tankyrase1 (TNKS1). The specific binding modes are investigated between the TNKS1 protein and nicotinamide isostere (ISX) which functions as an inhibitor of TNKS1. The stabilities of ISX-TNKS1 and AVA939-TNKS1 complexes are estimated by molecular dynamics (MD) simulations and free energy calculations; a good agreement with experimental results is reached.

Ligand Binding / Docking (Cont'd)

Identification of estrogen receptor α ligands with virtual screening techniques

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J. Mol. Graph. and Mod., **64**, 30-39, 2016.

Utilization of computer-aided molecular discovery methods in virtual screening (VS) is a cost-effective approach to identify novel bioactive small molecules. Unfortunately, no universal VS strategy can guarantee high hit rates for all biological targets, but each target requires distinct, fine-tuned solutions. Here, we have studied in retrospective manner the effectiveness and usefulness of common pharmacophore hypothesis, molecular docking and negative image-based screening as potential VS tools for a widely applied drug discovery target, estrogen receptor α (ER α).

Modeling of Platinum-Aryl Interaction with Amyloid- β Peptide

Matthew Turner, James A. Platts [Cardiff University], and Robert J. Deeth

J. Chem. Theor. and Comp., **12**, 1385–1392, 2016.

Ligand field molecular mechanics (LFMM), density functional theory (DFT), and semiempirical PM7 methods are used to study the binding of two Pt(II)-L systems to an N-terminal fragment of the amyloid- β peptide, where L = 2,2-bipyridyl or 1,10-phenanthroline. Molecular dynamics simulations are used to explore the conformational freedom of the peptide using LFMM combined with AMBER molecular mechanics parameters. We establish a modeling protocol, allowing for identification and analysis of favorable platinum-binding modes and peptide conformations.

Protein Structural Memory Influences Ligand Binding Mode(s) and Unbinding Rates

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J. Chem. Theor. and Comp., **12**, 1393–1399, 2016.

The binding of small molecules (e.g., natural ligands, metabolites, and drugs) to proteins governs most biochemical pathways and physiological processes. Here, we use molecular dynamics to investigate the unbinding of dimethyl sulfoxide (DMSO) from two distinct states of a small rotamase enzyme, the FK506-binding protein (FKBP). These states correspond to the FKBP protein relaxed with and without DMSO in the active site. Since the time scale of ligand unbinding (2–20 ns) is faster than protein relaxation (100 ns), a novel methodology is introduced to relax the protein without having to introduce an artificial constraint.

Ligand Binding Pathways of Clozapine and Haloperidol in the Dopamine D₂ and D₃ Receptors

Trayder Thomas, Yu Fang, Elizabeth Yuriev, and David K. Chalmers [Monash University]

J. Chem. Infor. and Mod., **56**, 308–321, 2016.

The binding of a small molecule ligand to its protein target is most often characterized by binding affinity and is typically viewed as an on/off switch. The more complex reality is that binding involves the ligand passing through a series of intermediate states between the solution phase and the fully bound pose. We have performed a set of 29 unbiased molecular dynamics simulations to model the binding pathways of the dopamine receptor antagonists clozapine and haloperidol binding to the D₂ and D₃ dopamine receptors.

Ligand Binding / Docking (Cont'd)

Novel Inhibitors for a Novel Binding Site in Respiratory Complex III

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[University of California One Shields Avenue]

J. Phys. Chem. B., **120**, 2701–2708, 2016.

A new binding site and potential novel inhibitors of the respiratory complex III are described. The site is located at the opposite side of the enzyme with respect to ubiquinol binding site (Q_o site), and distinctly different from both Q_o and Q_i sites (hence designated as Non-Q binding site, NQ). NQ site binding pocket extends up close to Phe90 residue, an internal switch (LH switch) that regulates electron transfer between heme b_L and heme b_H of the low potential redox chain.

Computational analysis of the CB1 carboxyl-terminus in the receptor-G protein complex

Joong-Youn Shim [University of North Carolina], Leepakshi Khurana and Debra A. Kendall

Proteins: Stru. Fun. & Bioinf., **84**, 532–543, 2016.

Despite the important role of the carboxyl-terminus (Ct) of the activated brain cannabinoid receptor one (CB1) in the regulation of G protein signaling, a structural understanding of interactions with G proteins is lacking. This is largely due to the highly flexible nature of the CB1 Ct that dynamically adapts its conformation to the presence of G proteins. In the present study, we explored how the CB1 Ct can interact with the G protein by building on our prior modeling of the CB1-Gi complex to incorporate a complete CB1 Ct (Glu416^{Ct}–Leu472^{Ct}).

Enzyme Catalysis

A Trapped Covalent Intermediate of a Glycoside Hydrolase on the Pathway to Transglycosylation. Insights from Experiments and Quantum Mechanics/Molecular Mechanics Simulations

Lluís Raich, Vladimir Borodkin, Wenxia Fang, Jorge Castro-López, Daan M. F. van Aalten, Ramón Hurtado-Guerrero, and Carme Rovira [Universitat de Barcelona]

J. Am. Chem. Soc., **138**, 3325–3332, 2016.

The conversion of glycoside hydrolases (GHs) into transglycosylases (TGs), i.e., from enzymes that hydrolyze carbohydrates to enzymes that synthesize them, represents a promising solution for the large-scale synthesis of complex carbohydrates for biotechnological purposes. However, the lack of knowledge about the molecular details of transglycosylation hampers the rational design of TGs. Here we present the first crystallographic structure of a natural glycosyl–enzyme intermediate (GEI) of *Saccharomyces cerevisiae* Gas2 in complex with an acceptor substrate and demonstrate, by means of QM / MM metadynamics simulations, that it is tuned for transglycosylation ($\Delta G^\ddagger = 12$ kcal/mol).

Modulating Enzyme Catalysis through Mutations Designed to Alter Rapid Protein Dynamics

Ioanna Zoi, Javier Suarez, Dimitri Antoniou, Scott A. Cameron, Vern L. Schramm, and Steven D. Schwartz [Albert Einstein College of Medicine]

J. Am. Chem. Soc., **138**, 3403–3409, 2016.

The relevance of sub-picosecond protein motions to the catalytic event remains a topic of debate. Heavy enzymes (isotopically substituted) provide an experimental tool for bond-vibrational links to enzyme catalysis. A recent transition path sampling study with heavy purine nucleoside phosphorylase (PNP) characterized the experimentally observed mass-dependent slowing of barrier crossing (Antoniou, D.; Ge, X.; Schramm, V. L.; Schwartz, S. D. *J. Phys. Chem. Lett.* **2012**, 3, 3538). Here we computationally identify second-sphere amino acid residues predicted to influence the freedom of the catalytic site vibrational modes linked to heavy enzyme effects in PNP.

Enzyme Catalysis (Cont'd)

Dynamical study, hydrogen bond analysis, and constant pH simulations of the beta carbonic anhydrase of *Methanobacterium thermoautotrophicum*

Fab rio Bracht [Universidade Federal do Rio de Janeiro] & Ricardo Bicca de Alencastro

J. Biomol. Stru. and Dyn., **34**, 259-271, 2016.

Within the five classes (α , β , γ , δ , and ζ) of carbonic anhydrases (CAs) the first two, containing mammal and plant representatives, are the most studied among all CAs. In this study, we have focused our investigation on the beta-class carbonic anhydrase of *Methanobacterium thermoautotrophicum*. We investigated both the importance of the Asp-Arg dyad near the catalytic zinc-bound water and the possible roles that water molecules within the active site and residues near the entrance of the catalytic cleft have on the first step of the enzyme's reaction mechanism.

Molecular mechanical properties of short-sequence peptide enzyme mimics

Tsukasa Takahashi, Bao C. Vo Ngo, Leyang Xiao, Gaurav Arya & Michael J. Heller [University of California San Diego]

J. Biomol. Stru. and Dyn., **34**, 463-474, 2016.

While considerable attempts have been made to recreate the high turnover rates of enzymes using synthetic enzyme mimics, most have failed and only a few have produced minimal reaction rates that can barely be considered catalytic. One particular approach we have focused on is the use of short-sequence peptides that contain key catalytic groups in close proximity. In this study, we designed six different peptides and tested their ability to mimic the catalytic mechanism of the cysteine proteases.

Stereoselectivity of phosphotriesterase with paraoxon derivatives: a computational study

Dongling Zhan, Shanshan Guan, Hanyong Jin, Weiwei Han [Jilin University, Changchun] & Song Wang

J. Biomol. Stru. and Dyn., **34**, 600-611, 2016.

The bacterial enzyme phosphotriesterase (PTE) exhibits stereoselectivity toward hydrolysis of chiral substrates with a preference for the S_p enantiomer. In this work, docking analysis and two explicit-solvent molecular dynamics (MD) simulations were performed to characterize and differentiate the structural dynamics of PTE bound to the S_p and R_p paraoxon derivative enantiomers (R_p -1 and S_p -1) hydrolyzed with distinct catalytic efficiencies. Comparative analysis of the molecular trajectories for PTE bound to R_p -1 and S_p -1 suggested that substrate binding induced conformational changes in the loops near the active site.

In silico study of subtilisin-like protease 1 (SUB1) from different *Plasmodium* species in complex with peptidyl-difluorostatones and characterization of potent pan-SUB1 inhibitors

Simone Brogi, Simone Giovani, Margherita Brindisi, Sandra Gemma, Ettore Novellino, Giuseppe Campiani [University of Siena], Michael J. Blackman, Stefania Butini

J. Mol.Graph. and Mod., **64**, 121-130, 2016.

Plasmodium falciparum subtilisin-like protease 1 (SUB1) is a novel target for the development of innovative antimalarials. We recently described the first potent difluorostatone-based inhibitors of the enzyme ((4S)-(N-((N-acetyl-L-lysyl)-L-isoleucyl-L-threonyl-L-alanyl)-2,2-difluoro-3-oxo-4-aminopentanoyl)glycine (**1**) and (4S)-(N-((N-acetyl-L-isoleucyl)-L-threonyl-L-alanyl)amino)-2,2-difluoro-3-oxo-4-aminopentanoyl)glycine (**2**)). As a continuation of our efforts towards the definition of the molecular determinants of enzyme-inhibitor interaction, we herein propose the first comprehensive computational investigation of the SUB1 catalytic core from six different *Plasmodium* species, using homology modeling and molecular docking approaches.

Enzyme Catalysis (Cont'd)

Comparative modeling and molecular dynamics suggest high carboxylase activity of the *Cyanobium* sp. CACIAM14 RbcL protein

Andrei Santos Siqueira, Alex Ranieri Jerônimo Lima, Leonardo Teixeira, Juliana Simão Nina de Azevedo, João Lídio da Silva Gonçalves Vianez Jr, Evonnildo Costa Gonçalves [Universidade Federal do Pará]

J. Mol.Mod., **22**, 68, 2016.

Rubisco catalyzes the first step reaction in the carbon fixation pathway, bonding atmospheric CO₂/O₂ to ribulose 1,5-bisphosphate; it is therefore considered one of the most important enzymes in the biosphere. Genetic modifications to increase the carboxylase activity of rubisco are a subject of great interest to agronomy and biotechnology, since this could increase the productivity of biomass in plants, algae and cyanobacteria and give better yields in crops and biofuel production. Thus, the aim of this study was to characterize in silico the catalytic domain of the rubisco large subunit (rbcL gene) of *Cyanobium* sp. CACIAM14, and identify target sites to improve enzyme affinity for ribulose 1,5-bisphosphate.

Probing the ATP-induced conformational flexibility of the PcrA helicase protein using molecular dynamics simulation

Anil R. Mhashal, Chandan Kumar Choudhury, Sudip Roy [National Chemical Laboratory, Pune]

J. Mol.Mod., **22**, 54, 2016.

Helicases are enzymes that unwind double-stranded DNA (dsDNA) into its single-stranded components. It is important to understand the binding and unbinding of ATP from the active sites of helicases, as this knowledge can be used to elucidate the functionality of helicases during the unwinding of dsDNA. In this work, we investigated the unbinding of ATP and its effect on the active-site residues of the helicase PcrA using molecular dynamic simulations. To mimic the unbinding process of ATP from the active site of the helicase, we simulated the application of an external force that pulls ATP from the active site and computed the free-energy change during this process.

Computational Studies of Candida Antarctica Lipase B to Test Its Capability as a Starting Point To Redesign New Diels–Alderase

Katarzyna Świderek and Vicent Moliner [Lodz University of Technology]

J. Phys. Chem. B., **120**, 2053–2070, 2016.

The design of new biocatalysts is a target that is receiving increasing attention. One of the most popular reactions in this regard is the Diels–Alder cycloaddition because of its applications in organic synthesis and the absence of efficient natural enzymes that catalyze it. In this paper, the possibilities of using the highly promiscuous *Candida Antarctica* lipase B as a protein scaffold to redesign a Diels–Alderase has been explored by means of theoretical quantum mechanics/molecular mechanics (QM/MM) molecular dynamics simulations.

Strategies to reduce end-product inhibition in family 48 glycoside hydrolases

Mo Chen, Lintao Bu, Markus Alahuhta, Roman Brunecky, Qi Xu, Vladimir V. Lunin, John W. Brady, Michael F. Crowley, Michael E. Himmel and Yannick J. Bomble [National Renewable Energy Laboratory, Golden]

Proteins: Stru. Fun. & Bioinf., **84**, 295–304, 2016.

Family 48 cellobiohydrolases are some of the most abundant glycoside hydrolases in nature. They are able to degrade cellulosic biomass and therefore serve as good enzyme candidates for biofuel production. Family 48 cellulases hydrolyze cellulose chains via a processive mechanism, and produce end products composed primarily of cellobiose as well as other cellooligomers (dp ≤ 4). The challenge of utilizing cellulases in biofuel production lies in their extremely slow turnover rate. In this study, we quantitatively evaluated the product inhibitory effect of four family 48 glycoside hydrolases using molecular dynamics simulations and product expulsion free-energy calculations.

Enzyme Catalysis (Cont'd)

New insight into the architecture of oxy-anion pocket in unliganded conformation of GAT domains: A MD-simulation study

Hridoy R. Bairagya [Indian Institute of Science, Bangalore] and Manju Bansal

Proteins: Stru. Fun. & Bioinf., **84**, 360–373, 2016.

Human Guanine Monophosphate Synthetase (hGMPS) converts XMP to GMP, and acts as a bifunctional enzyme with N-terminal “glutaminase” (GAT) and C-terminal “synthetase” domain. The enzyme is identified as a potential target for anti-cancer and immunosuppressive therapies. GAT domain of enzyme plays central role in metabolism, and contains conserved catalytic residues Cys104, His190, and Glu192. MD simulation studies on GAT domain suggest that position of oxyanion in unliganded conformation is occupied by one conserved water molecule (W1), which also stabilizes that pocket.

Protein-Protein Interactions

Understanding the fabric of protein crystals: computational classification of biological interfaces and crystal contacts

Guido Capitani [ETH Zurich], Jose M. Duarte, Kumaran Baskaran, Spencer Bliven, and Joseph C. Somody

Bioinformatics. **32**, 481-489, 2016.

Modern structural biology still draws the vast majority of information from crystallography, a technique where the objects being investigated are embedded in a crystal lattice. Given the complexity and variety of those objects, it becomes fundamental to computationally assess which of the interfaces in the lattice are biologically relevant and which are simply crystal contacts. Since the mid-1990s, several approaches have been applied to obtain high-accuracy classification of crystal contacts and biological protein–protein interfaces. This review provides an overview of the concepts and main approaches to protein interface classification.

Analysis of secondary structural and physicochemical changes in protein–protein complexes

N. Saranya, K.M. Saravanan, M. Michael Gromiha & S. Selvaraj [Bharathidasan University]

J. Biomol. Stru. and Dyn., **34**, 508-516, 2016.

Conformation switching in protein–protein complexes is considered important for the molecular recognition process. Overall analysis of 123 protein–protein complexes in a benchmark data-set showed that 6.8% of residues switched over their secondary structure conformation upon complex formation. Amino acid residue-wise preference for conformation change has been analyzed in binding and non-binding site residues separately. In this analysis, residues such as Ser, Leu, Glu, and Lys had higher frequency of secondary structural conformation change.

Molecular dynamics simulation of coarse-grained poly(L-lysine) dendrimers

Ali Rahimi, Sepideh Amjad-Iranagh, Hamid Modarress [Amirkabir University of Technology]

J. Mol.Mod., **22**, 59, 2016.

Poly(L-lysine) (PLL) dendrimer are amino acid based macromolecules and can be used as drug delivery agents. Their branched structure allows them to be functionalized by various groups to encapsulate drug agents into their structure. In this work, an attempt was made on all-atom simulation of PLL dendrimer of different generations. Based on all-atom results, a coarse-grained model of this dendrimer was designed and its parameters were determined, to be used for simulation of three generations of PLL dendrimer, at two pHs. Similar to the all-atom, the coarse-grained results indicated that by increasing the generation, the dendrimer becomes more spherical.

Enzyme Catalysis (Cont'd)

Determination of the protonation state of the Asp dyad: conventional molecular dynamics versus thermodynamic integration

Jinfeng Huang, Yali Zhu, Bin Sun, Yuan Yao, Junjun Liu
[Huazhong University of Science and Technology]

J. Mol.Mod., **22**, 58, 2016.

The protonation state of the Asp dyad is important as it can reveal enzymatic mechanisms, and the information this provides can be used in the development of drugs for proteins such as memapsin 2 (BACE-1), HIV-1 protease, and rennin. Conventional molecular dynamics (MD) simulations have been successfully used to determine the preferred protonation state of the Asp dyad. In the present work, we demonstrate that the results obtained from conventional MD simulations can be greatly influenced by the particular force field applied or the values used for control parameters.

Ultra-High-Throughput Structure-Based Virtual Screening for Small-Molecule Inhibitors of Protein-Protein Interactions

David K. Johnson and John Karanicolas [University of Kansas]

J.Chem. Infor. and Mod., **56**, 399–411, 2016.

Protein-protein interactions play important roles in virtually all cellular processes, making them enticing targets for modulation by small-molecule therapeutics: specific examples have been well validated in diseases ranging from cancer and autoimmune disorders, to bacterial and viral infections. Protein interaction sites are especially challenging for computational approaches, because the target protein surface often undergoes a conformational change to enable ligand binding; this confounds traditional approaches for virtual screening. Here, we demonstrate that these pockets can further be used to identify ligands that complement the protein surface.

Membrane Proteins and Lipid Peptide Interactions

Outer Membrane Protein Folding and Topology from a Computational Transfer Free Energy Scale

Meishan Lin, Dennis Gessmann, Hammad Naveed, and Jie Liang [University of Illinois at Chicago]

J. Am. Chem. Soc., **138**, 2592–2601, 2016.

Knowledge of the transfer free energy of amino acids from aqueous solution to a lipid bilayer is essential for understanding membrane protein folding and for predicting membrane protein structure. Here we report a computational approach that can calculate the folding free energy of the transmembrane region of outer membrane β -barrel proteins (OMPs) by combining an empirical energy function with a reduced discrete state space model. We quantitatively analyzed the transfer free energies of 20 amino acid residues at the center of the lipid bilayer of OmpLA.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular dynamics simulations on the interaction of the transmembrane Na_vAb channel with cholesterol and lipids in the membrane

Chonticha Suwattanasophon, Peter Wolschann & Roland Faller [University of California]

J. Biomol. Stru. and Dyn., **34**, 318-326, 2016.

Increased cholesterol levels are associated with multiple pathological conditions. In this work, molecular dynamics simulations were applied to observe the influence of membrane cholesterol levels on a voltage-gated sodium channel. Different lipid compositions are modeled around the channel to obtain information about the possible effects by which cholesterol influences Na_vAb channels. Cholesterol was normally not directly interacting with either the closed or inactivated conformation. Cholesterol increased lipid packing implying that it plays a crucial role in restricting lipid movement in the region around 1 nm of the channel in a 1-palmitoyl-2-oleoyl phosphatidylcholine matrix.

Study of curcumin behavior in two different lipid bilayer models of liposomal curcumin using molecular dynamics simulation

Seifollah Jalili [K. N. Toosi University of Technology] & Marzieh Saeedi

J. Biomol. Stru. and Dyn., **34**, 327-340, 2016.

Liposomal formulation of curcumin is an important therapeutic agent for the treatment of various cancers. Despite extensive studies on the biological effects of this formulation in cancer treatment, much remains unknown about curcumin-liposome interactions. Understanding how different lipid bilayers respond to curcumin molecule may help us to design more effective liposomal curcumin. Here, we used molecular dynamics simulation method to investigate the behavior of curcumin in two lipid bilayers commonly used in preparation of liposomal curcumin, namely dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylglycerol (DMPG).

All-atom molecular dynamics simulations of an artificial sodium channel in a lipid bilayer: the effect of water solvation/desolvation of the sodium ion

A.A. Skelton [University of KwaZulu Natal], V.M. Khedkar & J.R. Fried

J. Biomol. Stru. and Dyn., **34**, 529-539, 2016.

All-atom molecular dynamics is used to investigate the transport of Na⁺ across a 1,2-dioleoyl-sn-glycero-3-phosphocholine lipid bilayer facilitated by a diazacrown hydrapile. Specifically, the free energy of Na⁺ passing through the bilayer is calculated using the adaptive biasing force method to study the free energy associated with the increase in Na⁺ transport in the presence of the hydrapile molecule. The results show that water interaction greatly influences Na⁺ transport through the lipid bilayer as water is pulled through the bilayer with Na⁺ forming a water channel.

Curcumin specifically binds to the human calcium-calmodulin-dependent protein kinase IV: fluorescence and molecular dynamics simulation studies

Nasimul Hoda, Huma Naz, Ehtesham Jameel, Ashutosh Shandilya, Sharmistha Dey, Md. Imtaiyaz Hassan [Jamia Millia Islamia, Jamia Nagar], Faizan Ahmad & B. Jayaram

J. Biomol. Stru. and Dyn., **34**, 572-584, 2016.

Calcium-calmodulin-dependent protein kinase IV (CAMK4) plays significant role in the regulation of calcium-dependent gene expression, and thus, it is involved in varieties of cellular functions such as cell signaling and neuronal survival. On the other hand, curcumin, a naturally occurring yellow bioactive component of turmeric possesses wide spectrum of biological actions, and it is widely used to treat atherosclerosis, diabetes, cancer, and inflammation. It also acts as an antioxidant. Here, we studied the interaction of curcumin with human CAMK4 at pH 7.4 using molecular docking, MD simulations, fluorescence binding, and surface plasmon resonance (SPR) methods.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular dynamics simulations of Oxprenolol and Propranolol in a DPPC lipid bilayer

Khaled Azizi [University of Kurdistan, Sanandaj], Mokhtar Ganjali Koli

J. Mol.Graph. and Mod., **64**, 153-164, 2016.

Extensive microscopic molecular dynamics simulations have been performed to study the effects of two β -blocker drugs (Propranolol, Oxprenolol) on fully hydrated dipalmitoylphosphatidylcholine (DPPC) in the fluid phase at 323 K. Simulation of 4 systems containing varying concentrations of drugs was carried out. For the purpose of comparison, a fully hydrated DPPC bilayer without drugs was also studied at the same level of simulation technique which has been done on 4 other systems. The length of each simulation was 100 ns.

Principal Component Analysis of Lipid Molecule Conformational Changes in Molecular Dynamics Simulations

Pavel Buslaev, Valentin Gordeliy, Sergei Grudinin, and Ivan Gushchin [Moscow Institute of Physics and Technology]

J. Chem. Theor. and Comp., **12**, 1019–1028, 2016.

Molecular dynamics simulations of lipid bilayers are ubiquitous nowadays. Usually, either global properties of the bilayer or some particular characteristics of each lipid molecule are evaluated in such simulations, but the structural properties of the molecules as a whole are rarely studied. Here, we show how a comprehensive quantitative description of conformational space and dynamics of a single lipid molecule can be achieved via the principal component analysis (PCA).

Protein Folding

Folding of Protein L with Implications for Collapse in the Denatured State Ensemble

Hiranmay Maity and Govardhan Reddy [Indian Institute of Science, Bangalore]

J. Am. Chem. Soc., **138**, 2609–2616, 2016.

A fundamental question in protein folding is whether the coil to globule collapse transition occurs during the initial stages of folding (burst phase) or simultaneously with the protein folding transition. Single molecule fluorescence resonance energy transfer (FRET) and small-angle X-ray scattering (SAXS) experiments disagree on whether Protein L collapse transition occurs during the burst phase of folding. We study Protein L folding using a coarse-grained model and molecular dynamics simulations. The collapse transition in Protein L is found to be concomitant with the folding transition.

Accelerating Steered Molecular Dynamics: Toward Smaller Velocities in Forced Unfolding Simulations

Christian Mucksch and Herbert M. Urbassek [University of Kaiserslautern]

J. Chem. Theor. and Comp., **12**, 1380–1384, 2016.

The simulation of forced unfolding experiments, in which proteins are pulled apart, is conventionally done using steered molecular dynamics. We present here a hybrid scheme in which accelerated molecular dynamics is used together with steered molecular dynamics. We show that the new scheme changes the force–distance curves mainly in the region around the force maximum and thus demonstrate that the improved equilibration of the protein–solvent system brought about by using accelerated molecular dynamics makes the simulation more comparable to experimental data.

Protein Folding (Cont'd)

Information and redundancy in the burial folding code of globular proteins within a wide range of shapes and sizes

Diogo C. Ferreira, Marx G. van der Linden, Leandro C. de Oliveira, José N. Onuchic and Antônio F. Pereira de Araújo [Universidade De Brasília, Brasília]

Proteins: Stru. Fun. & Bioinf., **84**, 515–531, 2016.

Recent ab initio folding simulations for a limited number of small proteins have corroborated a previous suggestion that atomic burial information obtainable from sequence could be sufficient for tertiary structure determination when combined to sequence-independent geometrical constraints. Here, we use simulations parameterized by native burials to investigate the required amount of information in a diverse set of globular proteins comprising different structural classes and a wide size range. Burial information is provided by a potential term pushing each atom towards one among a small number L of equiprobable concentric layers.

Protein-Nucleic acid Interactions

catRAPID signature: identification of ribonucleoproteins and RNA-binding regions

Carmen Maria Livi, Petr Klus, Riccardo Delli Ponti, and Gian Gaetano Tartaglia [The Barcelona Institute of Science and Technology]

Bioinformatics. **32**, 773-775, 2016.

Recent technological advances revealed that an unexpected large number of proteins interact with transcripts even if the RNA-binding domains are not annotated. We introduce catRAPID signature to identify ribonucleoproteins based on physico-chemical features instead of sequence similarity searches. The algorithm, trained on human proteins and tested on model organisms, calculates the overall RNA-binding propensity followed by the prediction of RNA-binding regions. catRAPID signature outperforms other algorithms in the identification of RNA-binding proteins and detection of non-classical RNA-binding regions.

Molecular docking and dynamics simulations on the interaction of cationic porphyrin–anthraquinone hybrids with DNA G-quadruplexes

Muhammad Arba, Rahmana E. Kartasmita & Daryono H. Tjahjono [Bandung Institute of Technology]

J. Biomol. Stru. and Dyn., **34**, 427-438, 2016.

A series of cationic porphyrin–anthraquinone hybrids bearing either pyridine, imidazole, or pyrazole rings at the meso-positions have been investigated for their interaction with DNA G-quadruplexes by employing molecular docking and molecular dynamics simulations. Three types of DNA G-quadruplexes were utilized, which comprise parallel, antiparallel, and mixed hybrid topologies. The porphyrin hybrids have a preference to bind with parallel and mixed hybrid structures compared to the antiparallel structure.

Theoretical studies on binding modes of copper-based nucleases with DNA

Chunmei Liu, Yanyan Zhu, Mingsheng Tang [Zhengzhou University, Zhengzhou]

J. Mol.Graph. and Mod., **64**, 11-29, 2016.

In the present work, molecular simulations were performed for the purpose of predicting the binding modes of four types of copper nucleases (a total 33 compounds) with DNA. Our docking results accurately predicted the groove binding and electrostatic interaction for some copper nucleases with B-DNA. The intercalation modes were also reproduced by “gap DNA”. The obtained results demonstrated that the ligand size, length, functional groups and chelate ring size bound to the copper center could influence the binding affinities of copper nucleases.

Protein - Nucleic Acid Interactions (Cont'd)

A Flexible Domain-Domain Hinge Promotes an Induced-fit Dominant Mechanism for the Loading of Guide-DNA into Argonaute Protein in *Thermus thermophilus*

Lizhe Zhu, Hanlun Jiang, Fu Kit Sheong, Xuefeng Cui, Xin Gao, Yanli Wang, and Xuhui Huang [The Hong Kong University of Science and Technology]

J. Phys. Chem. B., **120**, 2709–2720, 2016.

Argonaute proteins (Ago) are core components of the RNA Induced Silencing Complex (RISC) that load and utilize small guide nucleic acids to silence mRNAs or cleave foreign DNAs. Despite the essential role of Ago in gene regulation and defense against virus, the molecular mechanism of guide-strand loading into Ago remains unclear. We explore such a mechanism in the bacterium *Thermus thermophilus* Ago (TtAgo), via a computational approach combining molecular dynamics, bias-exchange metadynamics, and protein–DNA docking. We show that apo TtAgo adopts multiple closed states that are unable to accommodate guide-DNA.

Nucleic Acids

On the Use of Molecular Dynamics Simulations for Probing Allostery through DNA

Tomáš Dršata, Marie Zgarbová, Petr Jurečka, Jiří Šponer, Filip Lankaš [Academy of Sciences of the Czech Republic]

Biophysical Journal., **110**, 874–876, 2016.

A recent study described an allosteric effect in which the binding of a protein to DNA is influenced by another protein bound nearby. The effect shows a periodicity of ~10 basepairs and decays with increasing protein-protein distance. As a mechanistic explanation, the authors reported a similar periodic, decaying pattern of the correlation coefficient between major groove widths inferred from a shorter molecular dynamics simulation. We show that in a state-of-the-art, microsecond-long simulation of the same DNA sequence, the periodicity of the correlation coefficient is not observed.

Theoretical study of excited states of DNA base dimers and tetramers using optimally tuned range-separated density functional theory

Haitao Sun, Shian Zhang, Cheng Zhong and Zhenrong Sun [East China Normal University]

J. Comp. Chem., **37**, 684–693, 2016.

Excited states of various DNA base dimers and tetramers including Watson-Crick H-bonding and stacking interactions have been investigated by time-dependent density functional theory using nonempirically tuned range-separated exchange (RSE) functionals. Significant improvements are found in the prediction of excitation energies and oscillator strengths, with results comparable to those of high-level coupled-cluster (CC) models (RI-CC2 and EOM-CCSD(T)). The optimally-tuned RSE functional significantly outperforms its non-tuned (default) version and widely-used B3LYP functional.

DNA Distortion Caused by Uracil-Containing Intrastrand Cross-Links

Cassandra D. M. Churchill, Leif A. Eriksson, and Stacey D. Wetmore [University of Lethbridge]

J. Phys. Chem. B., **120**, 1195–1204, 2016.

Four uracil-containing intrastrand cross-links have been detected in human cells upon UV irradiation of 5-bromouracil-containing DNA, namely 5'-G[8-5]U-3', 5'-U[5-8]G-3', 5'-A[8-5]U-3', and 5'-A[2-5]U-3'. These lesions feature unique composition and connectivity. For the first time, structural information obtained using MD simulations reveal that all four lesions distort the DNA helix, which can involve an extrahelical location of the cross-link, changes in the helical interactions of the complementary nucleotides, or disruption of hydrogen bonding in the flanking base pairs up to two positions from the cross-linked site.

2. METHODOLOGY

Quantitative Structure-Activity Relations

The effect of various atomic partial charge schemes to elucidate consensus activity-correlating molecular regions: a test case of diverse QSAR models

Sivakumar Prasanth Kumar, Prakash C. Jha, Yogesh T. Jasrai [Gujarat University] & Himanshu A. Pandya

J. Biomol. Stru. and Dyn., **34**, 540-559, 2016.

The estimation of atomic partial charges of the small molecules to calculate molecular interaction fields (MIFs) is an important process in field-based quantitative structure–activity relationship (QSAR). Several studies showed the influence of partial charge schemes that drastically affects the prediction accuracy of the QSAR model and focused on the selection of appropriate charge models that provide highest cross-validated correlation coefficient (r_{cv}^2 or q^2) to explain the variation in chemical structures against biological endpoints.

Potentials and Parameters

Accurately modeling nanosecond protein dynamics requires at least microseconds of simulation

Gregory R. Bowman [Washington University School of Medicine]

J. Comp. Chem., **37**, 558–566, 2016.

Advances in hardware and algorithms have greatly extended the timescales accessible to molecular simulation. This article assesses whether such long timescale simulations improve our ability to calculate order parameters that describe conformational heterogeneity on ps-ns timescales or if force fields are now a limiting factor. Order parameters from experiment are compared with order parameters calculated in three different ways from simulations ranging from 10 ns to 100 μ s in length.

Effect of TFE on the Helical Content of AK17 and HAL-1 Peptides: Theoretical Insights into the Mechanism of Helix Stabilization

Jiří Vymětal, Lucie Bednářová, and Jiří Vondrášek [AS CR, Flemingovo náměstí 2]

J. Phys. Chem. B., **120**, 1048–1059, 2016.

Fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) are among the most frequently used cosolvents in experiment studies of peptides. They have significant effects on secondary structure and a particularly strong promotion of α -helix is induced by TFE. In this study we validated recently proposed force field parameters for TFE in molecular dynamics simulations with two model peptides—alanine-rich AK-17 and antimicrobial peptide halictine-1 (HAL-1). In the case of HAL-1, we characterized the effect of TFE on this peptide experimentally by ECD spectroscopy.

Molecular Dynamics

Atomic-resolution dissection of the energetics and mechanism of isomerization of hydrated ATP-Mg²⁺ through the SOMA string method

Davide Branduardi, Fabrizio Marinelli and José D. Faraldo-Gómez [National Institutes of Health, Bethesda]

J. Comp. Chem., **37**, 575–586, 2016.

The atomic mechanisms of isomerization of ATP-Mg²⁺ in solution are characterized using the recently developed String Method with Optimal Molecular Alignment (SOMA) and molecular-dynamics simulations. Bias-Exchange Metadynamics simulations are first performed to identify the primary conformers of the ATP-Mg²⁺ complex and their connectivity. SOMA is then used to elucidate the minimum free-energy path (MFEP) for each transition, in a 48-dimensional space.

Importance of Hydrodynamic Interactions in the Stepping Kinetics of Kinesin

Yonathan Goldtzvik, Zhechun Zhang, and D. Thirumalai [University of Maryland, College Park]

J. Phys. Chem. B., **120**, 2071–2075, 2016.

Conventional kinesin walks by a hand-over-hand mechanism on the microtubule (MT) by taking ~8 nm discrete steps and consumes one ATP molecule per step. The time needed to complete a single step is on the order of 20 μs. We show, using simulations of a coarse-grained model of the complex containing the two motor heads, the MT and the coiled coil, that to obtain quantitative agreement with experiments for the stepping kinetics hydrodynamic interactions (HIs) have to be included. In simulations without hydrodynamic interactions, spanning nearly 20 μs, not a single step was completed in one hundred trajectories.

Monte Carlo Simulations of Glu-242 in Cytochrome c Oxidase

Benjamin M. Samudio, Vernon Couch, and Alexei A. Stuchebrukhov [University of California, Davis]

J. Phys. Chem. B., **120**, 2095–2105, 2016.

Monte Carlo (MC) simulations of conformational changes and protonation of Glu-242, a key residue that shuttles protons in cytochrome c oxidase (CcO), are reported. Previous studies suggest that this residue may play a role of the valve of the enzyme proton pump. Here we examine how sensitive the results of simulations are to the computational method used. We applied both molecular mechanic (MM) and hybrid quantum mechanic:molecular mechanic (QM:MM) methods and find that the results are qualitatively different.

Free Energy Perturbation

Free energies of solvation in the context of protein folding: Implications for implicit and explicit solvent models

Alexander Cumberworth, Jennifer M. Bui and Jörg Gsponer [Center for High-Throughput Biology, UBC, Vancouver]

J. Comp. Chem., **37**, 629–640, 2016.

Implicit solvent models for biomolecular simulations have been developed to use in place of more expensive explicit models; however, these models make many assumptions and approximations that are likely to affect accuracy. Here, the changes in free energies of solvation upon folding $\Delta\Delta G_{\text{solv}}$ of several fast folding proteins are calculated from previously run μs–ms simulations with a number of implicit solvent models and compared to the values needed to be consistent with the explicit solvent model used in the simulations.

QM and QM/MM

Theoretical investigation of fluorination effect on the charge carrier transport properties of fused anthra-tetrathiphenes and its derivatives

Jun Yin, Kadali Chaitanya, Xue-Hai Ju [Nanjing University of Science and Technology]

J. Mol. Graph. and Mod., **64**, 40-50, 2016.

The crystal structures of known anthra-tetrathiphenes (ATT) and its three fluorinated derivatives (ATT1, ATT2 and ATT3) were predicted by the Monte Carlo-simulated annealing method with the embedded electrostatic potential (ESP) charges. The most stable crystal structures were further optimized by the density functional theory with the dispersion energy (DFT-D) method. The effect of the electron-withdrawing fluorine atoms on the molecular geometry, molecular stacking, electronic and transport properties of title compounds were investigated by the density functional theory and the incoherent charge-hopping model.

Copper Oxidation/Reduction in Water and Protein: Studies with DFTB3/MM and VALBOND Molecular Dynamics Simulations

Haiyun Jin, Puja Goyal, Akshaya Kumar Das, Michael Gaus, Markus Meuwly, and Qiang Cui [University of Wisconsin—Madison]

J. Phys. Chem. B., **120**, 1894–1910, 2016.

We apply two recently developed computational methods, DFTB3 and VALBOND, to study copper oxidation/reduction processes in solution and protein. The properties of interest include the coordination structure of copper in different oxidation states in water or in a protein (plastocyanin) active site, the reduction potential of the copper ion in different environments, and the environmental response to copper oxidation.

How Can Linoleic Acid Be the Preferential Substrate of the Enzyme 15-Lipoxygenase-1? A QM/MM Approach

Jordi Soler, Patricia Saura, Diego García-López, Laura Masgrau, José M. Lluch, and Àngels González-Lafont [Universitat Autònoma de Barcelona]

J. Phys. Chem. B., **120**, 1950–1960, 2016.

The most common substrate of mammalian lipoxygenases (LOXs) is arachidonic acid (AA). However, 15-LOXs can present dual substrate specificity. These LOXs catalyze the peroxidation of AA, initiated by a H-abstraction step (mainly H₁₃-abstraction) by the Fe(III)–OH[−] cofactor, and the peroxidation of linoleic acid (LA) after H₁₁-abstraction. In this paper, QM(B3LYP)/MM(CHARMM) calculations of the rate-limiting H₁₁-abstraction process of LA catalyzed by rabbit 15-LOX-1 (15-rLOX-1) have been carried out using a complete model of the solvated 15-rLOX-1:LA complex.

Enhancing Paradynamics for QM/MM Sampling of Enzymatic Reactions

Jerônimo Lameira, Ilya Kupchenko, and Arie Warshel [University of Southern California]

J. Phys. Chem. B., **120**, 2155–2164, 2016.

Despite the enormous increase in computer power, it is still extremely challenging to obtain computationally converging sampling of ab initio QM/MM (QM(ai)/MM) free energy surfaces in condensed phases. The sampling problem can be significantly reduced by the use of the reference potential paradynamics (PD) approach, but even this approach still requires major computer time in studies of enzymatic reactions. To further reduce the sampling problem we developed here a new PD version where we use an empirical valence bond reference potential that has a minimum rather than a maximum at the transition state region of the target potential (this is accomplished conveniently by shifting the EVB of the product state).

Ligand Docking

Kinetics of a Multilamellar Lipid Vesicle Ripening: Simulation and Theory

Rui Xu and Xuehao He [Tianjin University]

J. Phys. Chem. B., **120**, 2262–2270, 2016.

Lipid vesicle ripening via unimolecular diffusion and exchange greatly influences the evolution of complex vesicle structure. However, this behavior is difficult to capture using conventional experimental technology and molecular simulation. In the present work, the ripening of a multilamellar lipid vesicle (MLV) is effectively explored using a mesoscale coarse-grained molecular model. The simulation reveals that a small MLV evolves into a unilamellar vesicle over a very long time period. In this process, only the outermost bilayer inflates, and the inner bilayers shrink.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 64, March, 2016.

- 1-10 **Recognition of halides and Y-shaped oxoanions by carbonylchromium-based urea-like molecules: A theoretical analysis of hydrogen bonding modes**, Chao Wang, Yizhong Yuan, Xiaohui Tian [East China University of Science and Technology], Rebecca L. Gieseck, Jinyu Sun

One of the major challenges in anion recognition is to design hosts that can be used to distinguish between anions of different shapes. Urea-based molecules are widely used in anion recognition because the pair of -NH groups acts as an electron acceptor. Although these hosts can bind to both spherical anions (halides) and Y-shaped anions (oxoanions), experimental evidence to date does not provide a clear picture of what differences in the nature of the hydrogen bonding interactions could be used to distinguish between anions of different shapes.

- 11-29 **Theoretical studies on binding modes of copper-based nucleases with DNA**, Chunmei Liu, Yanyan Zhu, Mingsheng Tang [Zhengzhou University, Zhengzhou]

See Applications / Protein-Nucleic acids.

- 30-39 **Identification of estrogen receptor α ligands with virtual screening techniques**, Sanna P. Niinivehmas, Elangovan Manivannan, Sanna Rauhamäki, Juhani Huuskonen, Olli T. Pentikäinen [University of Jyväskylä]

See Applications / Ligand Binding.

- 40-50 **Theoretical investigation of fluorination effect on the charge carrier transport properties of fused anthra-tetrathiophene and its derivatives**, Jun Yin, Kadali Chaitanya, Xue-Hai Ju [Nanjing University of Science and Technology]

See Methodology / QM and QM/MM.

- 51-59 **Experiment and DFT studies on radioiodine removal and storage mechanism by imidazolium-based ionic liquid**, Bobo Cao, Shuangyue Liu, Dongmei Du, Zhimin Xue, Hui Fu, Haitao Sun [Qufu Normal University, Qufu]

In order to remove and store radioactive substances effectively, studies on the mechanisms of radioiodine captured by ionic liquids (ILs) with a fixed cation (1-butyl-3-methyl-imidazolium cation [Bmim]⁺) were carried out in experimental and theoretical methods. Fourier transform infrared attenuated total reflectance (FT-IR ATR) spectra of 2BP8HQ and ultraviolet-visible (UV/vis) spectroscopy were used to investigate the kinetic process of radioiodine removal by ILs in experiment.

- 60-74 **Polyelectrolyte conformational transition in aqueous solvent mixture influenced by hydrophobic interactions and hydrogen bonding effects: PAA–water–ethanol**, Praveenkumar Sappidi, Upendra Natarajan [Indian Institute of Technology (IIT) Madras]

Molecular dynamics simulations of poly(acrylic acid) PAA chain in water–ethanol mixture were performed for un-ionized and ionized cases at different degree-of-ionization 0%, 80% and 100% of PAA chain by Na⁺ counter-ions and co-solvent (ethanol) concentration in the range 0–90 vol% ethanol.

- 75-84 **Molecular dynamics simulation of non-covalent single-walled carbon nanotube functionalization with surfactant peptides**, Abolfazl Barzegar [University of Tabriz], Alireza Mansouri, Jafar Azamat

See Applications / Carbon Nanotubes.

- 85-93 **Contribution of main chain and side chain atoms and their locations to the stability of thermophilic proteins**, Dharma Rao Tompa, M. Michael Gromiha, K. Saraboji [SASTRA University, Thanjavur]

See Applications / Protein Dynamics.

- 94-100 **Crystal morphology prediction of 1,3,3-trinitroazetidine in ethanol solvent by molecular dynamics simulation**, Wenyan Shi [Nanjing University of Science & Technology], Yuting Chu, Mingzhu Xia, Wu Lei, Fengyun Wang

In order to understand the mechanism of the effect of solvent on the crystal morphology of explosives, and be convenient for the choice of crystallization solvent, the attachment energy (AE) model was performed to predict the growth morphology and the main crystal faces of 1,3,3-trinitroazetidine (TNAZ) in vacuum. The molecular dynamics simulation was applied to investigate the interactions of TNAZ crystal faces and ethanol solvent, and the growth habit of TNAZ in ethanol solvent was predicted using the modified AE model.

- 101-109 **Design and synthesis of a novel class of carbonic anhydrase-IX inhibitor 1-(3-(phenyl/4-fluorophenyl)-7-imino-3H-[1,2,3]triazolo[4,5d]pyrimidin 6(7H)yl)urea**, Shikha Kumari, Danish Idrees, Chandra Bhushan Mishra, Amresh Prakash, Wahiduzzaman, Faizan Ahmad, Md. Imtaiyaz Hassan, Manisha Tiwari [University of Delhi]

See Applications / Medicinal Chemistry and Drug Design.

- 110-120 **Quantitative structure–hydrophobicity relationships of molecular fragments and beyond**, Jian-Wei Zou [Ningbo Institute of Technology], Meilan Huang, Jian-Xiang Huang, Gui-Xiang Hu, Yong-Jun Jiang

Quantitative structure-property relationship (QSPR) models were firstly established for the hydrophobic substituent constant (π_x) using the theoretical descriptors derived solely from electrostatic potentials (EPSs) at the substituent atoms. The descriptors introduced are found to be related to hydrogen-bond basicity, hydrogen-bond acidity, cavity, or dipolarity/polarizability terms in linear solvation energy relationship, which endows the models good interpretability.

- 121-130 **In silico study of subtilisin-like protease 1 (SUB1) from different Plasmodium species in complex with peptidyl-difluorostatones and characterization of potent pan-SUB1 inhibitors**, Simone Brogi, Simone Giovani, Margherita Brindisi, Sandra Gemma, Ettore Novellino, Giuseppe Campiani [University of Siena], Michael J. Blackman, Stefania Butini

See Applications / Enzyme Catalysis.

- 131-138 **Cationic P...N interaction in $\text{XH}_3\text{P}^+\cdots\text{NCY}$ complexes ($\text{X} = \text{H, F, CN, NH}_2, \text{OH}$; $\text{Y} = \text{H, Li, F, Cl}$) and its cooperativity with hydrogen/lithium/halogen bond**, Mehdi D. Esrafil [University of Maragheh], Soheila Asadollahi

The geometries, interaction energies and bonding properties of cationic pnictogen bond (CPB) interactions are studied in binary $\text{XH}_3\text{P}^+\cdots\text{NCY}$ ($\text{X} = \text{H, F, CN, NH}_2, \text{OH}$; $\text{Y} = \text{H, Li, F, Cl}$) complexes by means of MP2/aug-cc-pVTZ calculations.

- 139-146 **Ion- π interaction in impacting the nonlinear optical properties of ion-buckybowl complexes**, He Chen, Wen-Yong Wang, Li Wang, Chang-Li Zhu, Xin-Yan Fang, Yong-Qing Qiu [Northeast Normal University, Changchun]

Ion-buckybowl complexes have received considerable attention in modern chemical research due to its fundamental and practical importance. Herein, we performed density functional theory (DFT) to calculate the geometrical structure, binding interactions, dipole moments and the first hyperpolarizabilities (β_{tot}) of ion-buckybowl complexes (ions are Cl^- and Na^+ , buckybawls are quadrannulene, corannulene and sumanene).

- 147-152 **RADMAP: Simple probes for rapid assessment of complex reactivity: A method and case studies on the reaction of hydrogen atoms with unsaturated organic molecules**, Andrew K. Long, Jason A. Fawcett, Jason A.C. Clyburne, Cory C. Pye [Saint Mary's University, Halifax]

RADMAP, an open source program, allows for rapid analysis and visualization of the earliest stages of reactions between any molecule and a monoatomic probe (i.e., H^* , H^+ , H^- , Br^* , or any other monoatomic species) using ab initio methods. This program creates non-planar potential energy surfaces of the initial interaction between a molecule of interest and the monoatomic probe.

- 153-164 **Molecular dynamics simulations of Oxprenolol and Propranolol in a DPPC lipid bilayer**, Khaled Azizi [University of Kurdistan, Sanandaj], Mokhtar Ganjali Koli

See Applications / Membrane Proteins & Lipid Peptide Interactions.

Journal of Computational Chemistry, 37 (6), March, 2016.

- 550-557 **Multiscale enhanced sampling of intrinsically disordered protein conformations**, Kuo Hao Lee and Jianhan Chen [Kansas State University]

See Applications / Protein Conformational Analysis.

- 558-566 **Accurately modeling nanosecond protein dynamics requires at least microseconds of simulation**, Gregory R. Bowman [Washington University School of Medicine]

See Methodology / Potentials and Parameters.

- 567–574 **Comparative exploration of hydrogen sulfide and water transmembrane free energy surfaces via orthogonal space tempering free energy sampling**, Chao Lv, Erick W. Aitchison, Dongsheng Wu, Lianqing Zheng, Xiaolin Cheng and Wei Yang [Florida State University, Tallahassee]

Hydrogen sulfide (H_2S), a commonly known toxic gas compound, possesses unique chemical features that allow this small solute molecule to quickly diffuse through cell membranes. Taking advantage of the recent orthogonal space tempering (OST) method, we comparatively mapped the transmembrane free energy landscapes of H_2S and its structural analogue, water (H_2O), seeking to decipher the molecular determinants that govern their drastically different permeabilities.

- 575–586 **Atomic-resolution dissection of the energetics and mechanism of isomerization of hydrated ATP-Mg^{2+} through the SOMA string method**, Davide Branduardi, Fabrizio Marinelli and José D. Faraldo-Gómez [National Institutes of Health, Bethesda]

See Methodology / Molecular Dynamics.

- 587–594 **Coupled folding and binding with 2D Window-Exchange Umbrella Sampling**, Alex Dickson, Logan S. Ahlstrom and Charles L. Brooks III [The University of Michigan, Ann Arbor]

See Applications / Protein Dynamics.

- 595–601 **Self-guided Langevin dynamics via generalized Langevin equation**, Xiongwu Wu [National Institutes of Health (NIH), Bethesda], Bernard R. Brooks and Eric Vanden-Eijnden

See Applications / Protein Confirmation Analysis.

- 602–613 **Simulations of thermodynamics and kinetics on rough energy landscapes with milestoning**, Juan M. Bello-Rivas and Ron Elber [University of Texas at Austin]

We investigated by computational means the kinetics and stationary behavior of stochastic dynamics on an ensemble of rough two-dimensional energy landscapes. There are no obvious separations of temporal scales in these systems, which constitute a simple model for the behavior of glasses and some biomaterials.

- 614–622 **Free energy simulations with the AMOEBA polarizable force field and metadynamics on GPU platform**, Xiangda Peng, Yuebin Zhang, Huiying Chu and Guohui Li [Chinese Academy of Sciences, Dalian]

See Applications / Free Energy Calculations.

Journal of Computational Chemistry, 37 (7), March, 2016.

- 629–640 **Free energies of solvation in the context of protein folding: Implications for implicit and explicit solvent models**, Alexander Cumberworth, Jennifer M. Bui and Jörg Gsponer [Center for High-Throughput Biology, UBC, Vancouver]

See Methodology / Free Energy Perturbations.

- 641–652 **Application of zone-folding approach to the first-principles estimation of thermodynamic properties of carbon and ZrS₂-based nanotubes**, Andrei V. Bandura, Vitaly V. Porsev and Robert A. Evarestov [Saint-Petersburg State University]

A zone-folding (ZF) approach is applied for the estimation of the phonon contributions to thermodynamic properties of carbon- and ZrS₂-based nanotubes (NTs) of hexagonal morphology with different chiralities. The results obtained are compared with those from the direct calculation of the thermodynamic properties of NTs using PBE0 hybrid exchange-correlation functional.

- 653–664 **Hierarchical atom type definitions and extensible all-atom force fields**, Zhao Jin, Chunwei Yang, Fenglei Cao, Feng Li, Zhifeng Jing, Long Chen, Zhe Shen, Liang Xin, Sijia Tong and Huai Sun [Shanghai Jiao Tong University]

The extensibility of force field is a key to solve the missing parameter problem commonly found in force field applications. The extensibility of conventional force fields is traditionally managed in the parameterization procedure, which becomes impractical as the coverage of the force field increases above a threshold. A hierarchical atom-type definition (HAD) scheme is proposed to make extensible atom type definitions, which ensures that the force field developed based on the definitions are extensible.

- 665–674 **Moment expansion of the linear density-density response function**, Arne Scherrer and Daniel Sebastiani [Martin-Luther-University Halle-Wittenberg]

We present a low rank moment expansion of the linear density-density response function. The general interacting (fully nonlocal) density-density response function is calculated by means of its spectral decomposition via an iterative Lanczos diagonalization technique within linear density functional perturbation theory.

- 675–683 **UV-photoexcitation and ultrafast dynamics of HCFC-132b (CF₂ClCH₂Cl)**, Gessenildo Pereira Rodrigues, Elizete Ventura, Silmar Andrade do Monte and Mario Barbatti [Aix Marseille Université]

The UV-induced photochemistry of HCFC-132b (CF₂ClCH₂Cl) was investigated by computing excited-state properties with time-dependent density functional theory (TDDFT), multiconfigurational second-order perturbation theory (CASPT2), and coupled cluster with singles, doubles, and perturbative triples (CCSD(T)).

- 684–693 **Theoretical study of excited states of DNA base dimers and tetramers using optimally tuned range-separated density functional theory**, Haitao Sun, Shian Zhang, Cheng Zhong and Zhenrong Sun [East China Normal University]

See Applications / Nucleic Acids.

Journal of Computational Chemistry, 37 (8), March, 2016.

- 701–711 **Revisiting the concept of the (a)synchronicity of diels-alder reactions based on the dynamics of quasiclassical trajectories**, Miguel A. F. de Souza, Elizete Ventura, Silmar A. do Monte, José M. Riveros and Ricardo L. Longo [Universidade Federal De Pernambuco]

A number of model Diels-Alder (D-A) cycloaddition reactions ($\text{H}_2\text{C}=\text{CH}_2 + \text{cyclopentadiene}$ and $\text{H}_2\text{C}=\text{CHX} + 1,3\text{-butadiene}$, with $\text{X} = \text{H}, \text{F}, \text{CH}_3, \text{OH}, \text{CN}, \text{NH}_2, \text{and NO}$) were studied by static (transition state - TS and IRC) and dynamics (quasiclassical trajectories) approaches to establish the (a)synchronous character of the concerted mechanism.

- 712–723 **A highly efficient hybrid method for calculating the hydration free energy of a protein**, Hiraku Oshima and Masahiro Kinoshita [Kyoto University, Uji]

See Applications / Protein Dynamics.

- 724–738 **Sparsity-weighted outlier FLOODing (OFLOOD) method: Efficient rare event sampling method using sparsity of distribution**, Ryuhei Harada, Tomotake Nakamura and Yasuteru Shigeta [University of Tsukuba, Tsukuba]

As an extension of the Outlier FLOODing (OFLOOD) method [Harada et al., J. Comput. Chem. 2015, 36, 763], the sparsity of the outliers defined by a hierarchical clustering algorithm, FlexDice, was considered to achieve an efficient conformational search as sparsity-weighted “OFLOOD.” In OFLOOD, FlexDice detects areas of sparse distribution as outliers.

- 739–752 **Hybridizing rapidly exploring random trees and basin hopping yields an improved exploration of energy landscapes**, Christine-Andrea Roth, Tom Dreyfus, Charles H. Robert and Frédéric Cazals [Laboratoire De Biochimie Théorique]

The number of local minima of the potential energy landscape (PEL) of molecular systems generally grows exponentially with the number of degrees of freedom, so that a crucial property of PEL exploration algorithms is their ability to identify local minima, which are low lying and diverse. In this work, we present a new exploration algorithm, retaining the ability of basin hopping (BH) to identify local minima, and that of transition based rapidly exploring random trees (T-RRT) to foster the exploration of yet unexplored regions.

- 753–762 **Flexible CDOCKER: Development and application of a pseudo-explicit structure-based docking method within CHARMM**, Jessica K. Gagnon, Sean M. Law and Charles L. Brooks III [University of Michigan, Ann Arbor]

See Applications / Bioinformatics.

- 763–770 **Competition between hydrogen and halogen bonding in halogenated 1-methyluracil: Water systems**, Simon W.L. Hogan and Tanja van Mourik [University of St. Andrews, United Kingdom]

The competition between hydrogen- and halogen-bonding interactions in complexes of 5-halogenated 1-methyluracil (XmU ; $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}, \text{or At}$) with one or two water molecules in the binding region between C5-X and $\text{C4}=\text{O4}$ is investigated with M06-2X/6-31+G(d) .

- 771–779 **Recasting wave functions into valence bond structures: A simple projection method to describe excited states**, Julien Racine, Denis Hagebaum-Reignier, Yannick Carissan and Stéphane Humbel [Aix Marseille Université, CNRS]

A method is proposed to obtain coefficients and weights of valence bond (VB) determinants from multi configurational wave functions. This reading of the wave functions can apply to ground states as well as excited states.

Journal of Molecular Modeling, 22 (3), March, 2016.

- 68 **Comparative modeling and molecular dynamics suggest high carboxylase activity of the *Cyanobium* sp. CACIAM14 RbcL protein**, Andrei Santos Siqueira, Alex Ranieri Jerônimo Lima, Leonardo Teixeira, Juliana Simão Nina de Azevedo, João Lídio da Silva Gonçalves Vianez Jr, Evonnildo Costa Gonçalves [Universidade Federal do Pará]

See Applications / Enzyme Catalysis.

- 67 **Molecular dynamics study of the isothermal crystallization mechanism of polyethylene chain: the combined effects of chain length and temperature**, Rui Gao, Xuelian He, Haiyang Zhang, Yunqi Shao, Zhen Liu, Boping Liu [East China University of Science and Technology]

A molecular level understanding of the polyethylene (PE) crystallization process was elucidated by molecular dynamics simulation of three states, with varying chain length and temperature. The process can be classified into the following three states: (1) nucleation controlled state, (2) competitive state of crystal growth process and new nuclei formation, and (3) crystal growth controlled state, which could be quantified by the evolution of nuclei number.

- 66 **Dynamic mechanical characterization of CNT-PP nanocomposites**, A. Mandal [Indian Institute of Technology Delhi], S. P. Singh, R. Prasad

See Applications / Carbon Nanotubes.

- 65 **Comparative theoretical study of the structures and stabilities of four typical gadolinium carboxylates in different scintillator solvents**, Pin-Wen Huang [Zhejiang University of Water Resources and Electric Power]

The structural properties and stabilities of four typical gadolinium carboxylates (Gd-CBX) in toluene, linear alkyl benzene (LAB), and phenyl xylyl ethane (PXE) solvents were theoretically studied using density functional theory (DFT/B3LYP with the basis sets 6-311G(d) and MWB54) and the polarizable continuum model (PCM).

- 64 **Enhancing effect of metal coordination interaction on pnictogen bonding**, Qingjie Tang, Qingzhong Li [Yantai University]

The ternary complexes $ML \cdots PyZX_2 \cdots NH_3$ ($ML = CuCl, CuCN, AgCN, \text{ and } AuCN$; $Z = P, As, \text{ and } Sb$; $X = H \text{ and } F$) have been investigated with quantum chemical calculations. The results showed that the existence of coordination interaction has a prominent enhancing effect on the strength of pnictogen bonding.

- 63 **Ferromagnetic ground state for a hypothetical iron-based extended metal atom chain**, Paweł Szarek [University of Warsaw], Wojciech Wegner, Wojciech Grochala

Theoretical calculations for the first tri-iron-based extended metal atom chain (EMAC) molecule are reported. The studied triple-high-spin ($S = 6$) complex exhibits ferromagnetic ordering (according to Ising and spin-

projection approximations), which renders it unique among all previously prepared and theoretically calculated EMAC compounds.

- 62 **On the vibrational behavior of single- and double-walled carbon nanotubes under the physical adsorption of biomolecules in the aqueous environment: a molecular dynamics study**, S. Ajori [University of Guilan], R. Ansari, M. Darvizeh

See Applications / Carbon Nanotubes.

- 61 **Molecular dynamics simulations of a lithium/sodium carbonate mixture**, Alistar Ottochian, Chiara Ricca, Frederic Labat, Carlo Adamo [Institut Universitaire de France]

The diffusion and ionic conductivity of $\text{Li}_x\text{Na}_{1-x}\text{CO}_3$ salt mixtures were studied by means of Molecular Dynamics (MD) simulations, using the Janssen and Tissen model (Janssen and Tissen, *Mol Simul* 5:83–98; 1990). These salts have received particular attention due to their central role in fuel cells technology, and reliable numerical methods that could perform as important interpretative tool of experimental data are thus required but still lacking.

- 60 **Mechanisms and reactivity differences for the cobalt-catalyzed enantioselective intramolecular hydroacylation of ketones and alkenes: insights from density functional calculations**, Qingxi Meng [Shandong Agricultural University], Fen Wang

Density functional theory (DFT) was used to study the cobalt(I)-catalyzed enantioselective intramolecular hydroacylation of ketones and alkenes. All intermediates and transition states were fully optimized at the M06/6-31G(d,p) level (LANL2DZ(f) for Co). The results demonstrated that the ketone and alkene present different reactivities in the enantioselective hydroacylation.

- 59 **Molecular dynamics simulation of coarse-grained poly(L-lysine) dendrimers**, Ali Rahimi, Sepideh Amjad-Iranagh, Hamid Modarress [Amirkabir University of Technology]

See Methodology / Potentials and Parameters.

- 58 **Determination of the protonation state of the Asp dyad: conventional molecular dynamics versus thermodynamic integration**, Jinfeng Huang, Yali Zhu, Bin Sun, Yuan Yao, Junjun Liu [Huazhong University of Science and Technology]

See Methodology / Potentials and Parameters.

- 57 **Using the general-purpose reactivity indicator: challenging examples**, James S. M. Anderson [AICS, RIKEN, Kobe], Junia Melin, Paul W. Ayers

We elucidate the regioselectivity of nucleophilic attack on substituted benzenesulfonates, quinolines, and pyridines using a general-purpose reactivity indicator (GPRI) for electrophiles. We observe that the GPRI is most accurate when the incoming nucleophile resembles a point charge.

- 56 **DFT investigation on the decarboxylation mechanism of ortho hydroxy benzoic acids with acid catalysis**, Yanying Hu, Lu Gao, Zhoutong Dai, Guojuan Sun, Tongcun Zhang, Shiru Jia, Yujie Dai, Xiuli Zhan [Tianjin University of Science and Technology]

A density functional theory (DFT) study was performed to explore the mechanisms of the acid-catalyzed decarboxylation reaction of salicylic acids using the B3LYP method with 6-31++G(d,p) basis set in both gas phase and aqueous environment.

- 55 **Estimation of melting points of large set of persistent organic pollutants utilizing QSPR approach**, Marquita Watkins, Natalia Sizochenko, Bakhtiyor Rasulev, Jerzy Leszczynski [Jackson State University]

The presence of polyhalogenated persistent organic pollutants (POPs), such as Cl/Br-substituted benzenes, biphenyls, diphenyl ethers, and naphthalenes has been identified in all environmental compartments. The exposure to these compounds can pose potential risk not only for ecological systems, but also for human health.

- 54 **Probing the ATP-induced conformational flexibility of the PcrA helicase protein using molecular dynamics simulation**, Anil R. Mhashal, Chandan Kumar Choudhury, Sudip Roy [National Chemical Laboratory, Pune]

See Applications / Enzyme Catalysis.

- 53 **Mechanistic investigation of palladium-catalyzed amidation of aryl halides**, Yun Liang, Ying Ren, Jianfeng Jia, Hai-Shun Wu [Shanxi Normal University, Linfen]

A mechanistic investigation using Becke3LYP density functional theory (DFT) was carried out on the palladium-catalyzed amidation of bromobenzene and ^tBu-isocyanide. The whole catalytic cycle consists of five steps: oxidative addition, migratory insertion, anion exchange, reductive elimination, and hydrogen migration.

- 52 **Comparison of the directionality of the halogen, hydrogen, and lithium bonds between HOOOH and XF (X = Cl, Br, H, Li)**, Lixun Liu, Lingpeng Meng, Xueying Zhang, Yanli Zeng [Hebei Normal University]

Detailed electrostatic potential (ESP) analyses were performed to compare the directionality of halogen bonds with those of hydrogen bonds and lithium bonds. To do this, the interactions of HOOOH with the molecules XF (X = Cl, Br, H, Li) were investigated.

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About 95 Papers from more than 30 Journals are cited.

1	APPLICATIONS (61)	Page 2		
1.1	Small Molecules (15)			
	General and Model Systems	Page 2	QSAR	Page 6
	Med. Chem. And Drug Design	Page 3	Carbon Nanoparticles	Page 6
1.2	Biopolymers (43)			
	Bioinformatics and Cheminformatics	Page 7	Ligand Binding	Page 13
	Protein Secondary Structure	Page 8	Enzyme Catalysis	Page 14
	Comparative or Homology Modeling	Page 8	Protein-Protein Interactions	Page 16
	Protein Conformational Analysis	Page 8	Membrane Proteins	Page 17
	Protein Structure Analysis	Page 11	Protein Folding	Page 18
	Protein Dynamics	Page 11	Nucleic Acids	Page 18
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 19		
2	METHODOLOGY (20)	Page 19		
	QSAR	Page 19	QM & QM/MM	Page 21
	Potentials and Parameters	Page 20	Ligand Docking Modeling	Page 23
	Molecular Dynamics	Page 20		
3	JOURNAL REVIEWS (5)	Page 25		
	Journal of Molecular Graphics and Modeling, 65, April, 2016.			
	Journal of Computational Chemistry, 37 (9), April, 2016.			
	Journal of Computational Chemistry, 37 (10), April, 2016.			
	Journal of Computational Chemistry, 37 (11), April, 2016.			
	Journal of Molecular Modeling, 22 (4), April, 2016.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 36		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

A new algorithm for construction of coarse-grained sites of large biomolecules

Min Li, John Z. H. Zhang and Fei Xia [NYU-ECNU Center for Computational Chemistry at NYU Shanghai]

J. Comp. Chem., **37**, 795–804, 2016.

The development of coarse-grained (CG) models for large biomolecules remains a challenge in multiscale simulations, including a rigorous definition of CG representations for them. In this work, we proposed a new stepwise optimization imposed with the boundary-constraint (SOBC) algorithm to construct the CG sites of large biomolecules, based on the scheme of essential dynamics CG. By means of SOBC, we can rigorously derive the CG representations of biomolecules with less computational cost. The SOBC is particularly efficient for the CG definition of large systems with thousands of residues.

Constructing Optimal Coarse-Grained Sites of Huge Biomolecules by Fluctuation Maximization

Min Li, John Zenghui Zhang, and Fei Xia [East China Normal University]

J. Chem. Theor. and Comp., **12**, 2091–2100, 2016.

Coarse-grained (CG) models are valuable tools for the study of functions of large biomolecules on large length and time scales. The definition of CG representations for huge biomolecules is always a formidable challenge. In this work, we propose a new method called fluctuation maximization coarse-graining (FM-CG) to construct the CG sites of biomolecules. The defined residual in FM-CG converges to a maximal value as the number of CG sites increases, allowing an optimal CG model to be rigorously defined on the basis of the maximum.



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Medicinal Chemistry and Drug Design

Development of a potent 2-oxoamide inhibitor of secreted phospholipase A₂ guided by molecular docking calculations and molecular dynamics simulations

Sofia Vasilakaki, Efrosini Barbayianni, Georgios Leonis, Manthos G. Papadopoulos, Thomas Mavromoustakos, Michael H. Gelb, George Kokotos [Kapodistrian University of Athens]

Bioorg. and Med. Chem., **24**, 1683-1695, 2016.

Inhibition of group IIA secreted phospholipase A₂ (GIIA sPLA₂) has been an important objective for medicinal chemists. We have previously shown that inhibitors incorporating the 2-oxoamide functionality may inhibit human and mouse GIIA sPLA₂s. Herein, the development of new potent inhibitors by molecular docking calculations using the structure of the known inhibitor **7** as scaffold, are described. Synthesis and biological evaluation of the new compounds revealed that the long chain 2-oxoamide based on (S)-valine **GK241** led to improved activity (IC₅₀ = 143 nM and 68 nM against human and mouse GIIA sPLA₂, respectively).

A mixed DFT-MD methodology for the in silico development of drug releasing macrocycles. Calix and thia-calix[N]arenes as carriers for Bosutinib and Sorafenib

Rodrigo Galindo-Murillo, Luis Enrique Aguilar-Suárez and Joaquín Barroso-Flores [Centro Conjunto De Investigación En Química Sustentable UAEM-UNAM]

J. Comp. Chem., **37**, 940–946, 2016.

Interaction energies between a family of 36 calix[n]arenes, their corresponding thia- analogues, and two commercially available second generation tyrosine kinase III inhibitors—Bosutinib and Sorafenib—were calculated through DFT methods at the B97D/6-31G(d,p) level of theory, based on Natural Population Analysis, for the in silico development of suitable drug carriers based on the aforementioned macrocycles which can increase their bioavailability and in turn their pharmaceutical efficiency.

Discovery of a Novel, Orally Efficacious Liver X Receptor (LXR) β Agonist

Yajun Zheng, Linghang Zhuang, Kristi Yi Fan, Colin M. Tice, Wei Zhao, Chengguo Dong, Stephen D. Lotesta, Katerina Leftheris, Peter R. Lindblom, Zhijie Liu, Jun Shimada, Paul B. Noto, Shi Meng, Andrew Hardy, Lamont Howard, Paula Krosky, Joan Guo, Kerri Lipinski, Geeta Kandpal, Yuri Bukhtiyarov, Yi Zhao, Deepak Lala, Rebecca Van Orden, Jing Zhou, Guozhou Chen, Zhongren Wu, Brian M. McKeever, Gerard M. McGeehan, Richard E. Gregg, David A. Claremon, and Suresh B. Singh [Vitae Pharmaceuticals, Inc.]

Jou. Med. Chem., **59**, 3264–3271, 2016.

This article describes the application of Contour to the design and discovery of a novel, potent, orally efficacious liver X receptor β (LXR β) agonist (**17**). Contour technology is a structure-based drug design platform that generates molecules using a context perceptive growth algorithm guided by a contact sensitive scoring function. The growth engine uses binding site perception and programmable growth capability to create drug-like molecules by assembling fragments that naturally complement hydrophilic and hydrophobic features of the protein binding site. Starting with a crystal structure of LXR β and a docked 2-(methylsulfonyl)benzyl alcohol fragment (**6**), Contour was used to design agonists containing a piperazine core.

Medicinal Chemistry and Drug Design (Cont'd)

Docking and ADMET prediction of few GSK-3 inhibitors divulges 6-bromoindirubin-3-oxime as a potential inhibitor

Chaluveelaveedu Murleedharan Nisha, Ashwini Kumar, Archana Vimal, Bhukya Mounika Bai, Dharm Pal, Awanish Kumar [National Institute of Technology, Raipur]

J. Mol.Graph. and Mod., **65**, 100-107, 2016.

GSK-3 is a member of cellular kinases with diversified functions such as cellular differentiation, metabolic signaling, neuronal functions and apoptosis. It has been validated as an important therapeutic target in Alzheimer's disease and type 2 diabetes. Few molecules targeting GSK-3 are currently in clinical trials. In this study, we have compared certain docking and computational ADME (Absorption, Distribution, Metabolism, Excretion) parameters of a few GSK-3 targeted ligands (Indirubin, Hymenialdisine, Meridianins, 6-bromoindirubin-3-oxime) against two control molecules (Tideglusib and LY-2090314) to derive and analyze the basic drug-like properties of the test compounds.

Exploring isoxazole and carboxamide derivatives as potential non-nucleoside reverse transcriptase inhibitors

Sudheer S. Kurup, Kaustubh A. Joshi [Institute of Chemical Technology, Nathalal Parekh Marg]

J. Mol.Graph. and Mod., **65**, 113-128, 2016.

Nonnucleoside reverse transcriptase inhibitors (NNRTI) are a class of drug molecules with a specific target of HIV-1 reverse transcriptase (RT). In the present work, we evaluated a set of selected oxazole and carboxamide derivatives to identify potential pharmacophoric features using molecular docking approach. The docking approach employed has been validated by enrichment factor calculation at top 1% (EF_{1%}). It shows a considerable improvement in EF_{1%} value compared to earlier reported study carried out on specific dataset of ligands and decoys for RT, in the directory of useful decoys (DUD).

Investigation of the effect of erythrosine B on amyloid beta peptide using molecular modeling

Juho Lee, Inchan Kwon, Seung Soon Jang, Art E. Cho [Korea University, Sejong]

J. Mol.Mod., **22**, 92, 2016.

Neurotoxic plaques composed of 39 to 42 residue-long amyloid beta peptides (A β s) are copiously present in the brains of patients with Alzheimer's disease (AD). Erythrosine B (ER), a xanthene food dye, inhibits the formation of A β fibrils and A β -associated cytotoxicity in vitro. Here, in an attempt to elucidate the inhibition mechanism, we performed molecular dynamics (MD) simulations to demonstrate the conformational change of A β 40 induced by ER molecules in atomistic detail.

Free energy calculation provides insight into the action mechanism of selective PARP-1 inhibitor

Ran Cao [Peking Union Medical College]

J. Mol.Mod., **22**, 74, 2016.

Selective poly (ADP-ribose) polymerase (PARP)-1 inhibitor represents promising therapy against cancers with a good balance between efficacy and safety. Owing to the conserved structure between PARP-1 and PARP-2, most of the clinical and experimental drugs show equivalent inhibition against both targets. Most recently, it's disclosed a highly selective PARP-1 inhibitor (NMS-P118) with promising pharmacokinetic properties. Herein, we combined molecular simulation with free energy calculation to gain insights into the selective mechanism of NMS-P118.

Medicinal Chemistry and Drug Design (Cont'd)

Discovery of Novel Nonactive Site Inhibitors of the Prothrombinase Enzyme Complex

Karan Kapoor, Nicole McGill, Cynthia B. Peterson, Harold V. Meyers, Michael N. Blackburn, and Jerome Baudry [University of Tennessee, Knoxville]

J.Chem. Infor. and Mod., **56**, 535–547, 2016.

The risk of serious bleeding is a major liability of anticoagulant drugs that are active-site competitive inhibitors targeting the Factor Xa (FXa) prothrombin (PT) binding site. The present work identifies several new classes of small molecule anticoagulants that can act as nonactive site inhibitors of the prothrombinase (PTase) complex composed of FXa and Factor Va (FVa). These new classes of anticoagulants were identified, using a novel agnostic computational approach to identify previously unrecognized binding pockets at the FXa-FVa interface.

Identification of New Human Malaria Parasite Plasmodium falciparum Dihydroorotate Dehydrogenase Inhibitors by Pharmacophore and Structure-Based Virtual Screening

Elumalai Pavadai, Farah El Mazouni, Sergio Wittlin, Carmen de Kock, Margaret A. Phillips, and Kelly Chibale [University of Cape Town]

J.Chem. Infor. and Mod., **56**, 548–562, 2016.

Plasmodium falciparum dihydroorotate dehydrogenase (PfDHODH), a key enzyme in the de novo pyrimidine biosynthesis pathway, which the Plasmodium falciparum relies on exclusively for survival, has emerged as a promising target for antimalarial drugs. In an effort to discover new and potent PfDHODH inhibitors, 3D-QSAR pharmacophore models were developed based on the structures of known PfDHODH inhibitors and the validated Hypo1 model was used as a 3D search query for virtual screening of the National Cancer Institute database.

Computer Simulation Studies of the Mechanism of Hydrotrope-Assisted Solubilization of a Sparingly Soluble Drug Molecule

Shubhadip Das and Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **120**, 3540–3550, 2016.

The effect of hydrotrope sodium cumene sulfonate (SCS) on the solubility of a sparingly water-soluble drug, griseofulvin, is studied by employing classical molecular dynamics simulation technique. We mainly focus on the underlying mechanism by which SCS enhances the solubility of a sparingly soluble or insoluble solute in water. The main observations are the following: (a) The self-aggregation of SCS molecules (through its hydrophobic tail) above the minimum hydrotrope concentration (MHC) causes the formation of micellar-like frameworks.

Quantitative Structure-Activity Relations

Compound profiling and 3D-QSAR studies of hydrazone derivatives with activity against intracellular *Trypanosoma cruzi*

Lívia Bandeira Costa, Marcos Veríssimo de Oliveira Cardoso, Gevanio Bezerra de Oliveira Filho, Paulo André Teixeira de Moraes Gomes, José Wanderlan Pontes Espíndola, Thays Gabrielle de Jesus Silva, Pedro Henrique Monteiro Torres, Floriano Paes Silva Junior, Julio Martin, Regina Célia Bressan Queiroz de Figueiredo, Ana Cristina Lima Leite [Universidade Federal de Pernambuco]

Bioorg. and Med. Chem., **24**, 1608-1618, 2016.

Chagas disease is a tropical disease caused by the parasite *Trypanosoma cruzi*, which is endemic in Central and South America. Few treatments are available with effectiveness limited to the early (acute) stage of disease, significant toxicity and widespread drug resistance. In this work we report the outcome of a HTS-ready assay chemical library screen to identify novel, nontoxic, small-molecule inhibitors of *T. cruzi*. We have selected 50 compounds that possess hydrazone as a common group. The compounds were screened using recombinant *T. cruzi* (Tulahuen strain) expressing beta-galactosidase. A 3D quantitative structure-activity relationship (QSAR) analysis was performed using descriptors calculated from comparative molecular field analysis (CoMFA).

Exploiting Multiple Descriptor Sets in QSAR Studies

Jabed H. Tomal, William J. Welch [The University of British Columbia], and Ruben H. Zamar

J.Chem. Infor. and Mod., **56**, 501-509, 2016.

A quantitative structure-activity relationship (QSAR) is a model relating a specific biological response to the chemical structures of compounds. There are many descriptor sets available to characterize chemical structure, raising the question of how to choose among them or how to use all of them for training a QSAR model. Making efficient use of all sets of descriptors is particularly problematic when active compounds are rare among the assay response data. We consider various strategies to make use of the richness of multiple descriptor sets when assay data are poor in active compounds.

Carbon Nanoparticles

Spontaneous Unzipping of Xylonucleic Acid Assisted by a Single-Walled Carbon Nanotube: A Computational Study

Soumadwip Ghosh and Rajarshi Chakrabarti [Indian Institute of Technology Bombay]

J. Phys. Chem. B., **120**, 3642-3652, 2016.

Xenonucleic acids are synthetic nucleic acid analogues that are potential candidates for antisense or antigene therapy owing to their higher thermal and enzymatic stability compared to that of naturally occurring ones at physiological conditions. We investigate the binding and unzipping of xylonucleic acid (XNA) containing xylose (a stereoisomer of ribose) sugar in its backbone assisted by a single walled carbon nanotube (SWCNT) using extensive atomistic molecular dynamics simulations.

1.2. Biopolymers

Bioinformatics and Cheminformatics

iBET: Immersive visualization of biological electron-transfer dynamics

C. Masato Nakano, Erick Moen, Hye Suk Byun, Heng Ma, Bradley Newman, Alexander McDowell, Tao Wei, Mohamed Y. El-Naggar [University of Southern California]

J. Mol.Graph. and Mod., **65**, 94-99, 2016.

Recently, we presented a computational framework named VizBET to simulate and visualize biological electron-transfer (ET) dynamics. The visualization process was encapsulated as a plugin to the Visual Molecular Dynamics (VMD) software. However, the user's ability to understand complex, multidimensional ET pathways was severely limited when visualized in 2D on traditional computer monitors. To provide a more accurate representation with enhanced depth perception, we here present an extension of VizBET named iBET to render the VMD model of ET dynamics in a commodity virtual reality (VR) platform.

KRAKENX: software for the generation of alignment-independent 3D descriptors

Vishwesh Venkatraman, Bjørn Kåre Alsberg [Norwegian University of Science and Technology]

J. Mol.Mod., **22**, 93, 2016.

The KRAKENX software calculates a large variety of molecular descriptors based on quantum chemistry computations. The program supports over 2000 three-dimensional descriptors that are calculated from the output of different quantum chemistry packages. The current implementation supports semi-empirical MOPAC-based computations and primarily focuses on orientation-independent descriptors that have been discussed in the literature. The descriptor performance has been exemplified using a number of large and diverse datasets and can be seen to produce parsimonious linear models.

First Multitarget Chemo-Bioinformatic Model To Enable the Discovery of Antibacterial Peptides against Multiple Gram-Positive Pathogens

Alejandro Speck-Planche [University of Santiago de Compostela (USC)], Valeria V. Kleandrova, Juan M. Ruso, and M. N. D. S. Cordeiro

J.Chem. Infor. and Mod., **56**, 588–598, 2016.

Antimicrobial peptides (AMPs) have emerged as promising therapeutic alternatives to fight against the diverse infections caused by different pathogenic microorganisms. In this context, theoretical approaches in bioinformatics have paved the way toward the creation of several *in silico* models capable of predicting antimicrobial activities of peptides. All current models have several significant handicaps, which prevent the efficient search for highly active AMPs. Here, we introduce the first multitarget (mt) chemo-bioinformatic model devoted to performing alignment-free prediction of antibacterial activity of peptides against multiple Gram-positive bacterial strains.

Protein Secondary Structure

PDP-CON: prediction of domain/linker residues in protein sequences using a consensus approach

Piyali Chatterjee, Subhadip Basu [Jadavpur University],
Julian Zubek,
Mahantapas Kundu, Mita Nasipuri, Dariusz Plewczynski

The prediction of domain/linker residues in protein sequences is a crucial task in the functional classification of proteins, homology-based protein structure prediction, and high-throughput structural genomics. In this work, a novel consensus-based machine-learning technique was applied for residue-level prediction of the domain/linker annotations in protein sequences using ordered/disordered regions along protein chains and a set of physicochemical properties.

J. Mol.Mod., **22**, 72, 2016.

Comparative or Homology Modeling

Isatin analogs as novel inhibitors of Candida spp. β -carbonic anhydrase enzymes

Atilla Akdemir, Özlen Güzel-Akdemir, Nilgün Karalı,
Claudiu T. Supuran [Sezione di Scienza Farmaceutiche]

Bioorg. and Med. Chem., **24**, 1648-1652, 2016.

Enzyme inhibition data of structurally novel isatin-containing sulfonamides were determined for two carbonic anhydrases (CAs, EC 4.2.1.1) from pathogenic Candida species (CaNce103 from *C. albicans* and CgNce103 from *C. glabrata*). The compounds show K_i values in the low nanomolar range for the fungal CAs, while they have significantly higher K_i values for the human CAs. Homology models were constructed for the CaNce103 and CgNce103 and subsequently the ligands were docked into these models to rationalize their enzyme inhibitory properties.

Protein Confirmation Analysis

Insights on the structural perturbations in human MTHFR Ala222Val mutant by protein modeling and molecular dynamics

P.A. Abhinand, Faraz Shaikh, Soumendranath Bhakat, Ashish Radadiya, L.V.K.S. Bhaskar, Anamik Shah & P.K. Ragunath
[Sri Ramachandra University, Porur]

J. Biomol. Stru. and Dyn., **34**, 892-905, 2016.

Methylenetetrahydrofolate reductase (MTHFR) protein catalyzes the only biochemical reaction which produces methyltetrahydrofolate, the active form of folic acid essential for several molecular functions. The Ala222Val polymorphism of human MTHFR encodes a thermolabile protein associated with increased risk of neural tube defects and cardiovascular disease. The three-dimensional structure of human MTHFR protein was obtained through homology modeling, by taking the MTHFR structures from *Escherichia coli* and *Thermus thermophilus* as templates.

Protein Conformational Analysis (Cont'd)

Effective protein conformational sampling based on predicted torsion angles

Yuedong Yang and Yaoqi Zhou [Griffith University]

J. Comp. Chem., **37**, 976–980, 2016.

Protein structure prediction is a long-standing problem in molecular biology. Due to lack of an accurate energy function, it is often difficult to know whether the sampling algorithm or the energy function is the most important factor for failure of locating near-native conformations of proteins. This article examines the size dependence of sampling effectiveness by using a perfect “energy function”: the root-mean-squared distance from the target native structure. Using protein targets up to 460 residues from critical assessment of structure prediction techniques (CASP11, 2014), we show that the accuracy of near native structures sampled is relatively independent of protein sizes but strongly depends on the errors of predicted torsion angles.

Why do the outer membrane proteins OmpF from *E. coli* and OprP from *P. aeruginosa* prefer trimers? Simulation studies

Jitti Niramitranon, Mark SP Sansom, Prapasiri Pongprayoon [Kasetsart University]

J. Mol.Graph. and Mod., **65**, 1-7, 2016.

Porins are water-filled protein channels across the outer membrane of gram-negative bacteria. Solutes are filtered by a constriction loop L3 at the mid of a pore. Porins are heat-stable and resistant to toxic agents and detergents. Most porins are trimer, but no clear explanation why trimeric form is preferable. In this work, we thus studied effects of oligomerization on porin structure and function in microscopic detail. A well-studied OmpF (general porin from *Escherichia coli*) and well-characterised OprP (phosphate-specific pore from *Pseudomonas aeruginosa*) are used as samples from 2 types of porins found in gram-negative bacteria.

Conformational changes of A β (1–42) monomers in different solvents

Myeongsang Lee, Hyun Joon Chang, Jung Yeon Park, Joonha Shin, Jong Woo Park, Jee Woo Choi, Jae In Kim, Sungsoo Na [Korea University]

J. Mol.Graph. and Mod., **65**, 8-14, 2016.

Amyloid proteins are known to be the main cause of numerous degenerative and neurodegenerative diseases. In general, amyloids are misfolded from monomers and they tend to have β -strand formations. These misfolded monomers are then transformed into oligomers, fibrils, and plaques. It is important to understand the forming mechanism of amyloids in order to prevent degenerative diseases to occur. A β protein is a highly noticeable protein which causes Alzheimer's disease. It is reported that solvents affect the forming mechanism of A β amyloids.

Mapping the intrinsically disordered properties of the flexible loop domain of Bcl-2: a molecular dynamics simulation study

Ian Ilizaliturri-Flores, José Correa-Basurto, Martiniano Bello, Jorge L. Rosas-Trigueros, Beatriz Zamora-López, Claudia G. Benítez-Cardoza, Absalom Zamorano-Carrillo [Ciudad de México]

J. Mol.Mod., **22**, 98, 2016.

Most of the B-cell lymphoma-2 (Bcl-2) protein structure has been elucidated; however, the conformation of its flexible loop domain (FLD) has not yet been experimentally predicted. Its high flexibility under physiological conditions is the reason. FLD behaves as an intrinsically disordered region (IDR) and can adopt regular structures in particular conditions associated with the control of Bcl-2's anti-apoptotic functions. Herein, an average model was obtained for the native Bcl-2 protein by homology modeling and MD simulation techniques. From this, only the atomic coordinates corresponding to the rFLD were simulated for 1 μ s by MD at 310 K.

Protein Conformational Analysis (Cont'd)

Structural Insight for Roles of DR5 Death Domain Mutations on Oligomerization of DR5 Death Domain–FADD Complex in the Death-Inducing Signaling Complex Formation: A Computational Study

Hongyi Yang, Yuhua Song [The University of Alabama at Birmingham]

J. Mol.Mod., **22**, 89, 2016.

Death receptor 5 (DR5)-induced apoptosis that prioritizes the death of tumor cells has been proposed as one of the promising cancer therapies. In this process, oligomerized DR5 death domain (DD) binding to Fas-associated death domain (FADD) leads to FADD activating caspase-8, which marks the formation of the death-inducing signaling complex (DISC) that initiates apoptosis. This study sought to provide structural and molecular insight for the roles of four selected DR5 DD mutations (E355K, E367K, K415N, and L363F) in the oligomerization of DR5 DD–FADD complex during the DISC formation.

Conformational flexibility of DENV NS2B/NS3pro: from the inhibitor effect to the serotype influence

Erika Piccirillo, Benjamin Merget, Christoph A. Sotriffer, Antonia T. do Amaral [Universidade de São Paulo]

J.Comp.Aided. Mol.des. **30**, 251-270, 2016.

The dengue virus (DENV) has four well-known serotypes, namely DENV1 to DENV4, which together cause 50–100 million infections worldwide each year. DENV NS2B/NS3pro is a protease recognized as a valid target for DENV antiviral drug discovery. However, NS2B/NS3pro conformational flexibility, involving in particular the NS2B region, is not yet completely understood and, hence, a big challenge for any virtual screening (VS) campaign. Molecular dynamics (MD) simulations were performed in this study to explore the DENV3 NS2B/NS3pro binding-site flexibility and obtain guidelines for further VS studies.

Temperature-Dependent Conformational Properties of Human Neuronal Calcium Sensor-1 Protein Revealed by All-Atom Simulations

Yuzhen Zhu, Buyong Ma, Ruxi Qi, Ruth Nussinov, and Qingwen Zhang [Shanghai University of Sport]

J. Phys. Chem. B., **120**, 3551–3559, 2016.

Neuronal calcium sensor-1 (NCS-1) protein has orthologues from *Saccharomyces cerevisiae* to human with highly conserved amino acid sequences. NCS-1 is an important factor controlling the animal's response to temperature change. This leads us to investigate the temperature effects on the conformational dynamics of human NCS-1 at 310 and 316 K by all-atom molecular dynamics (MD) simulations and dynamic community network analysis. Four independent 500 ns MD simulations show that secondary structure content at 316 K is similar to that at 310 K, whereas the global protein structure is expanded.

Protein Structure Analysis

KMAD: knowledge-based multiple sequence alignment for intrinsically disordered proteins

Joanna Lange, Lucjan S. Wyrwicz, and Gert Vriend [CMBI Radboudumc]

Bioinformatics. **32**, 932-936, 2016.

Intrinsically disordered proteins (IDPs) lack tertiary structure and thus differ from globular proteins in terms of their sequence–structure–function relations. IDPs have lower sequence conservation, different types of active sites and a different distribution of functionally important regions, which altogether make their multiple sequence alignment (MSA) difficult. The KMAD MSA software has been written specifically for the alignment and annotation of IDPs. It augments the substitution matrix with knowledge about post-translational modifications, functional domains and short linear motifs.

Automatic generation of bioinformatics tools for predicting protein–ligand binding sites

Yusuke Komiyama, Masaki Banno, Kokoro Ueki, Gul Saad, and Kentaro Shimizu [University of Tokyo, Bunkyo-ku]

Bioinformatics. **32**, 901-907, 2016.

Coarse grain (CG) models allow long-scale simulations with a much lower computational cost than that of all-atom simulations. However, the absence of atomistic detail impedes the analysis of specific atomic interactions that are determinant in most interesting biomolecular processes. In order to study these phenomena, it is necessary to reconstruct the atomistic structure from the CG representation. This structure can be analyzed by itself or be used as an onset for atomistic molecular dynamics simulations. In this work, we present a computer program that accurately reconstructs the atomistic structure from a CG model for proteins, using a simple geometrical algorithm.

Protein Dynamics

Monomerization alters the dynamics of the lid region in Campylobacter jejuni CstII: an MD simulation study

Pradeep Kumar Prabhakar, Alka Srivastava, K. Krishnamurthy Rao & Petety V. Balaji [Indian Institute of Technology Bombay]

J. Biomol. Stru. and Dyn., **34**, 778-791, 2016.

CstII, a bifunctional (α 2,3/8) sialyltransferase from *Campylobacter jejuni*, is a homotetramer. It has been reported that mutation of the interface residues Phe121 (F121D) or Tyr125 (Y125Q) leads to monomerization and partial loss of enzyme activity, without any change in the secondary or tertiary structures. MD simulations of both tetramer and monomer, with and without bound donor substrate, were performed for the two mutants and WT to understand the reasons for partial loss of activity due to monomerization since the active site is located within each monomer.

Implicit solvent coarse-grained model of polyamidoamine dendrimers: Role of generation and pH

Leebyn Chong, Fikret Aydin and Meenakshi Dutt [Rutgers the State University of New Jersey]

J. Comp. Chem., **37**, 920–926, 2016.

Highly branched polymers such as polyamidoamine (PAMAM) dendrimers are promising macromolecules in the realm of nanobiotechnology due to their high surface coverage of tunable functional groups. Modeling efforts of PAMAM can provide structural and morphological properties, but the inclusion of solvents and the exponential growth of atoms with generations make atomistic simulations computationally expensive. We apply an implicit solvent coarse-grained model, called the Dry Martini force field, to PAMAM dendrimers.

Protein Dynamics (Cont'd)

Impacts of the charged residues mutation S48E/N62H on the thermostability and unfolding behavior of cold shock protein: insights from molecular dynamics simulation with Gō model

Ji-Guo Su, Xiao-Ming Han, Shu-Xin Zhao, Yan-Xue Hou, Xing-Yuan Li, Li-Sheng Qi, Ji-Hua Wang [Dezhou University]

J. Mol.Mod., **22**, 91, 2016.

The cold shock protein from the hyperthermophile *Thermotoga maritima* (Tm-Csp) exhibits significantly higher thermostability than its homologue from the thermophile *Bacillus caldolyticus* (Bc-Csp). Experimental studies have shown that the electrostatic interactions unique to Tm-Csp are responsible for improving its thermostability. In the present work, the favorable charged residues in Tm-Csp were grafted into Bc-Csp by a double point mutation of S48E/N62H, and the impacts of the mutation on the thermostability and unfolding/folding behavior of Bc-Csp were then investigated by using a modified Gō model, in which the electrostatic interactions between charged residues were considered in the model.

Interplay between Two Allosteric Sites and Their Influence on Agonist Binding in Human μ Opioid Receptor

Damian Bartuzi [Medical University of Lublin], Agnieszka A. Kaczor, and Dariusz Matosiuk

J.Chem. Infor. and Mod., **56**, 563–570, 2016.

Allostery is a widespread mechanism that allows for precise protein tuning. Its underlying mechanisms are elusive, particularly when there are multiple allosteric sites at the protein. This concerns also G-protein-coupled receptors (GPCRs), which are targets for a vast part of currently used drugs. To address this issue, we performed molecular dynamics simulations of a GPCR–human μ opioid receptor (MOR) in a native-like environment, with full agonist (R)-methadone, Na⁺ ions, and a positive modulator BMS986122 in various configurations.

A β -solenoid model of the Pmel17 repeat domain: insights to the formation of functional amyloid fibrils

Nikolaos N. Louros, Fotis A. Baltoumas, Stavros J. Hamodrakas, Vassiliki A. Iconomidou [University of Athens]

J.Comp.Aided. Mol.des. **30**, 153-164, 2016.

Pmel17 is a multidomain protein involved in biosynthesis of melanin. This process is facilitated by the formation of Pmel17 amyloid fibrils that serve as a scaffold, important for pigment deposition in melanosomes. Here, we examine the structure of the RPT domain by performing sequence threading. The resulting model was subjected to energy minimization and validated through extensive molecular dynamics simulations.

Protein-Style Dynamical Transition in a Non-Biological Polymer and a Non-Aqueous Solvent

E. Mamontov [Oak Ridge National Laboratory], V. K. Sharma, J. M. Borreguero, and M. Tyagi

J. Phys. Chem. B., **120**, 3232–3239, 2016.

Temperature-dependent onset of apparent anharmonicity in the microscopic dynamics of hydrated proteins and other biomolecules has been known as protein dynamical transition for the last quarter of a century. Using neutron scattering and molecular dynamics simulation, techniques most often associated with protein dynamical transition studies, we have investigated the microscopic dynamics of one of the most common polymers, polystyrene, which was exposed to toluene vapor, mimicking the process of protein hydration from water vapor.

Ligand Binding/Docking

Computational full electron structure study of biological activity in Cyclophilin A

Wenjin Zhou [Oakland University, Rochester], Allison M. Rossetto, Xiaodong Pang & Linxiang Zhou

J. Biomol. Stru. and Dyn., **34**, 870-876, 2016.

Cyclosporine (CsA) is widely used in organ transplant patients to help prevent the patient's body from rejecting the organ. CsA has been shown to be a safe and highly effective immunosuppressive drug that binds with the protein Cyclophilin A (CypA) at active sites. However, the exact mechanism of this binding at the molecular level remains unknown. In this project, we elucidate the binding of CsA to CypA at the molecular level by computing their electron structures and revealing their interactions.

Computational studies on receptor–ligand interactions between novel buffalo (*Bubalus bubalis*) nucleotide-binding oligomerization domain-containing protein 2 (NOD2) variants and muramyl dipeptide (MDP)

Biswajit Brahma, Mahesh Chandra Patra, Purusottam Mishra, Bidhan Chandra De, Sushil Kumar, Jitendra Maharana, Ashutosh Vats, Sonika Ahlawat, Tirtha Kumar Datta, Sachinandan De [National Dairy Research Institute, Karnal]

J. Mol.Graph. and Mod., **65**, 15-26, 2016.

Nucleotide binding and oligomerization domain 2 (NOD2), a member of intracellular NOD-like receptors (NLRs) family, recognizes the bacterial peptidoglycan, muramyl dipeptide (MDP) and initiates host immune response. The precise ligand recognition mechanism of NOD2 has remained elusive, although studies have suggested leucine rich repeat (LRR) region of NOD2 as the possible binding site of MDP. In this study, we identified multiple transcripts of NOD2 gene in buffalo (buNOD2) and at least five LRR variants (buNOD2-LRRW (wild type), buNOD2-LRRV1-V4) were found to be expressed in buffalo peripheral blood mononuclear cells.

Homology modeling, docking, and molecular dynamics simulation of the receptor GALR2 and its interactions with galanin and a positive allosteric modulator

Wen-Qi Hui, Qi Cheng, Tian-Yu Liu, Qin Ouyang [Third Military Medical University]

J. Mol.Mod., **22**, 90, 2016.

Galanin receptor type 2 (GALR2) is a class A G-protein-coupled receptor (GPCR), and it has been reported that orthosteric ligands and positive allosteric modulators (PAMs) of GALR2 could potentially be used to treat epilepsy. So far, the X-ray structure of this receptor has not been resolved, and knowledge of the 3D structure of GALR2 may prove informative in attempts to design novel ligands and to explore the mechanism for the allosteric modulation of this receptor. In this study, homology modeling was used to obtain several GALR2 models using known templates.

Functional analysis of the binding model of microbial inulinases using docking and molecular dynamics simulation

Puneet Kumar Singh, Josmi Joseph, Sukriti Goyal, Abhinav Grover, Pratyoo Shukla [Maharshi Dayanand University]

J. Mol.Mod., **22**, 69, 2016.

Recently inulinase has regained interest due to its usage in the production of fructooligosaccharides, biofuels, and in pharmaceutical industries. Inulinases properties are experimentally reported by numerous studies but their characteristics are just partially explained by only a few computational investigations. In the present study we have investigated exoinulinase and endoinulinase from different microbial sources toward their catalytic activity. Docking and molecular dynamic (MD) simulation were carried out for microbial endoinulinase and exoinulinase docked with 1-kestose and fructose-6-phosphate respectively.

Ligand Binding / Docking (Cont'd)

Optimized Virtual Screening Workflow for the Identification of Novel G-Quadruplex Ligands

Teresa Kaserer, Riccardo Rigo, Philipp Schuster, Stefano Alcaro, Claudia Sissi, and Daniela Schuster [University of Innsbruck]

J.Chem. Infor. and Mod., **56**, 484–500, 2016.

G-quadruplexes, alternative DNA secondary structures present in telomeres, emerge as promising targets for the treatment of cancer, because they prevent telomere elongation and accordingly cell proliferation. Within this study, theoretically validated pharmacophore- and shape-based models as well as a theoretically validated docking protocol were generated and applied in parallel for virtual screening and the identification of novel G-quadruplex ligands. Top-ranked hits retrieved with all methods independently and in addition in a consensus approach were selected for biological testing.

Molecular Dynamics Analysis of Binding of Kinase Inhibitors to WT EGFR and the T790M Mutant

Jiyong Park, Joseph J. McDonald, Russell C. Petter, and K. N. Houk [University of California, Los Angeles]

J. Chem. Theor. and Comp., **12**, 2066–2078, 2016.

Epidermal growth factor receptor (EGFR) inhibitors interrupt EGFR-dependent cellular signaling pathways that lead to accelerated tumor growth and proliferation. Mutation of a threonine in the inhibitor binding pocket, known as the “gatekeeper”, to methionine (T790M) confers acquired resistance to several EGFR-selective inhibitors. We studied interactions between EGFR inhibitors and the gatekeeper residues of the target protein. Thermodynamic integration (TI) with Amber14 indicates that the binding energies of gefitinib and AEE788 to the active state of the T790M mutant EGFR is 3 kcal/mol higher than to the wild type (WT), whereas ATP binding energy to the mutant is similar to the WT.

Enzyme Catalysis

Insights into the structure and inhibition of *Giardia intestinalis* arginine deiminase: homology modeling, docking, and molecular dynamics studies

Pedro Josué Trejo-Soto, Rodrigo Aguayo-Ortiz, Lilián Yépez-Mulia, Alicia Hernández-Campos, José Luis Medina-Franco & Rafael Castillo [Universidad Nacional Autónoma de México]

J. Biomol. Stru. and Dyn., **34**, 732-748, 2016.

Giardia intestinalis arginine deiminase (GiADI) is an important metabolic enzyme involved in the energy production and defense of this protozoan parasite. The lack of this enzyme in the human host makes GiADI an attractive target for drug design against *G. intestinalis*. One approach in the design of inhibitors of GiADI could be computer-assisted studies of its crystal structure, such as docking; however, the required crystallographic structure of the enzyme still remains unresolved. Because of its relevance, in this work, we present a three-dimensional structure of GiADI obtained from its amino acid sequence using the homology modeling approximation.

Enzyme Catalysis (Cont'd)

Exploration of the chlorpyrifos escape pathway from acylpeptide hydrolases using steered molecular dynamics simulations

Dongmei Wang, Hanyong Jin, Junling Wang, Shanshan Guan, Zuoming Zhang & Weiwei Han [Jilin University]

J. Biomol. Stru. and Dyn., **34**, 749-761, 2016.

Acylpeptide hydrolases (APH) catalyze the removal of an N-acylated amino acid from blocked peptides. APH is significantly more sensitive than acetylcholinesterase, a target of Alzheimer's disease, to inhibition by organophosphorus (OP) compounds. Thus, OP compounds can be used as a tool to probe the physiological functions of APH. Here, we report the results of a computational study of molecular dynamics simulations of APH bound to the OP compounds and an exploration of the chlorpyrifos escape pathway using steered molecular dynamics (SMD) simulations.

Understanding the Mechanism of the Hydrogen Abstraction from Arachidonic Acid Catalyzed by the Human Enzyme 15-Lipoxygenase-2. A Quantum Mechanics/Molecular Mechanics Free Energy Simulation

Reynier Suardíaz, Pablo G. Jambrina, Laura Masgrau, Àngels González-Lafont, Edina Rosta [King's College London], and José M. Lluch

J. Chem. Theor. and Comp., **12**, 2079–2090, 2016.

Lipoxygenases (LOXs) are a family of enzymes involved in the biosynthesis of several lipid mediators. In the case of human 15-LOX, the 15-LOX-1 and 15-LOX-2 isoforms show slightly different reaction regioselectivity and substrate specificity, indicating that substrate binding and recognition may be different, a fact that could be related to their different biological role. Here, we have used long molecular dynamics simulations, QM(DFT)/MM potential energy and free energy calculations (using the newly developed DHAM method), to investigate the binding mode of the arachidonic acid (AA) substrate into 15-LOX-2 and the rate-limiting hydrogen-abstraction reaction 15-LOX-2 catalyzes.

Nonequilibrium Relaxation of Conformational Dynamics Facilitates Catalytic Reaction in an Elastic Network Model of T7 DNA Polymerase

Ziqing W. Zhao, X. Sunney Xie, and Hao Ge [Peking University]

J. Phys. Chem. B., **120**, 2869–2877, 2016.

Nucleotide-induced conformational closing of the finger domain of DNA polymerase is crucial for its catalytic action during DNA replication. Such large-amplitude molecular motion is often not fully accessible to either direct experimental monitoring or molecular dynamics simulations. However, a coarse-grained model can offer an informative alternative, especially for probing the relationship between conformational dynamics and catalysis. Here we investigate the dynamics of T7 DNA polymerase catalysis using a Langevin-type elastic network model incorporating detailed structural information on the open conformation without the substrate bound.

Theoretical Study of the Mechanism of Exemestane Hydroxylation Catalyzed by Human Aromatase Enzyme

Ignacio Viciano and Sergio Martí [Universitat Jaume I]

J. Phys. Chem. B., **120**, 3331–3343, 2016.

Human aromatase (CYP19A1) aromatizes the androgens to form estrogens via a three-step oxidative process. The estrogens are necessary in humans, mainly in women, because of the role they play in sexual and reproductive development. However, these also are involved in the development and growth of hormone-dependent breast cancer. In this study, the hydroxylation of exemestane catalyzed by aromatase has been studied by means of hybrid QM/MM methods.

Enzyme Catalysis (Cont'd)

Protein–Support Interactions for Rationally Designed Bilirubin Oxidase Based Cathode: A Computational Study

Ivana Matanovic, Sofia Babanova, Madelaine Seow Chavez, and Plamen Atanassov [University of New Mexico, Albuquerque]

J. Phys. Chem. B., **120**, 3634–3641, 2016.

An example of biocathode based on bilirubin oxidase (BOx) was used to demonstrate how density functional theory can be combined with docking simulations in order to study the interface interactions between the enzyme and specifically designed electrode surface. The electrode surface was modified through the adsorption of bilirubin, the natural substrate for BOx, and the prepared electrode was electrochemically characterized using potentiostatic measurements. The experimentally determined current densities showed that the presence of bilirubin led to significant improvement of the cathode operation.

Protein-Protein Interactions

DeNovo: virus-host sequence-based protein–protein interaction prediction

Fatma-Elzahraa Eid [Department of Computer Science], Mahmoud ElHefnawi, and Lenwood S. Heath

Bioinformatics. **32**, 1144–1150, 2016.

Can we predict protein–protein interactions (PPIs) of a novel virus with its host? Three major problems arise: the lack of known PPIs for that virus to learn from, the cost of learning about its proteins and the sequence dissimilarity among viral families that makes most methods inapplicable or inefficient. We develop DeNovo, a sequence-based negative sampling and machine learning framework that learns from PPIs of different viruses to predict for a novel one, exploiting the shared host proteins. We tested DeNovo on PPIs from different domains to assess generalization.

The role of protein “Stability patches” in molecular recognition: A case study of the human growth hormone-receptor complex

Roman Osman, Mihaly Mezei and Stanislav Engel [Ben-Gurion University of the Negev]

J. Comp. Chem., **37**, 913–919, 2016.

Dynamic characteristics of protein surfaces are among the factors determining their functional properties, including their potential participation in protein-protein interactions. The presence of clusters of static residues—“stability patches” (SPs)—is a characteristic of protein surfaces involved in intermolecular recognition. The mechanism, by which SPs facilitate molecular recognition, however, remains unclear. Analyzing the surface dynamic properties of the growth hormone and of its high-affinity variant we demonstrated that reshaping of the SPs landscape may be among the factors accountable for the improved affinity of this variant to the receptor.

Protein-Protein Interactions (Cont'd)

Focused grid-based resampling for protein docking and mapping

Artem B. Mamonov, Mohammad Moghadasi, Hanieh Mirzaei, Shahrooz Zarbafian, Laurie E. Grove, Tanggis Bohnuud, Pirooz Vakili, Ioannis Ch. Paschalidis, Sandor Vajda and Dima Kozakov [Stony Brook University]

J. Comp. Chem., **37**, 961–970, 2016.

The fast Fourier transform (FFT) sampling algorithm has been used with success in application to protein-protein docking and for protein mapping, the latter docking a variety of small organic molecules for the identification of binding hot spots on the target protein. Here we explore the local rather than global usage of the FFT sampling approach in docking applications. If the global FFT based search yields a near-native cluster of docked structures for a protein complex, then focused resampling of the cluster generally leads to a substantial increase in the number of conformations close to the native structure.

Membrane Proteins and Lipid Peptide Interactions

Automatic generation of bioinformatics tools for predicting protein–ligand binding sites

Yusuke Komiyama, Masaki Banno, Kokoro Ueki, Gul Saad, and Kentaro Shimizu [University of Tokyo, Bunkyo-ku]

Bioinformatics. **32**, 901–907, 2016.

Predictive tools that model protein–ligand binding on demand are needed to promote ligand research in an innovative drug-design environment. However, it takes considerable time and effort to develop predictive tools that can be applied to individual ligands. We developed a system for automatically generating protein–ligand binding predictions. Implementation of this system in a pipeline of Semantic Web technique-based web tools will allow users to specify a ligand and receive the tool within 0.5–1 day.

Machine Learning Based Dimensionality Reduction Facilitates Ligand Diffusion Paths Assessment: A Case of Cytochrome P450cam

J. Rydzewski [Nicolaus Copernicus University] and W. Nowak

J. Chem. Theor. and Comp, **12**, 2110–2120, 2016.

In this work we propose an application of a nonlinear dimensionality reduction method to represent the high-dimensional configuration space of the ligand–protein dissociation process in a manner facilitating interpretation. Rugged ligand expulsion paths are mapped into 2-dimensional space. The mapping retains the main structural changes occurring during the dissociation. The topological similarity of the reduced paths may be easily studied using the Fréchet distances, and we show that this measure facilitates machine learning classification of the diffusion pathways.

Protein Folding

CHARMM TIP3P Water Model Suppresses Peptide Folding by Solvating the Unfolded State

Sander Boonstra, Patrick R. Onck, and Erik van der Giessen
[University of Groningen]

J. Phys. Chem. B., **120**, 3692–3698, 2016.

The accuracy of molecular dynamics simulations depends on the underlying force field, defined by the form and parametrization of the interparticle potential functions and the water model. The treatment of the solvent is crucial in molecular dynamics force fields, as hydrophobic interactions and hydrogen bonding are important molecular forces. The latest version, CHARMM36, was optimized using the standard TIP3P water model (sTIP3P) for proteins, while mTIP3P is still being used for lipids. Our replica exchange molecular dynamics simulations on dynamic peptides show that the CHARMM36 force field with mTIP3P water yields less realistic folding than with sTIP3P water.

A hidden aggregation-prone structure in the heart of hypoxia inducible factor prolyl hydroxylase

Hamid Hadi-Alijanvand, Elizabeth A. Proctor, Feng Ding, Nikolay V. Dokholyan and Ali A. Moosavi-Movahedi
[University of Tehran]

Proteins: Stru. Fun. & Bioinf., **84**, 611–623, 2016.

Prolyl hydroxylase domain-containing protein 2 (PHD2), as one of the most important regulators of angiogenesis and metastasis of cancer cells, is a promising target for cancer therapy drug design. Progressive studies imply that abnormality in PHD2 function may be due to misfolding. Therefore, study of the PHD2 unfolding pathway paves the way for a better understanding of the influence of PHD2 mutations and cancer cell metabolites on the protein folding pathway. We study the unfolding of the PHD2 catalytic domain using differential scanning calorimetry (DSC), fluorescence spectroscopy, and discrete molecular dynamics simulations (DMD).

Nucleic Acids

The systematic approach to describing conformational rearrangements in G-quadruplexes

Vladimir Tsvetkov, Galina Pozmogova & Anna Varizhuk
[SRI of Physical-Chemical Medicine]

J. Biomol. Stru. and Dyn., **34**, 705-715, 2016.

Conformational changes in DNA G-quadruplex (GQ)-forming regions affect genome function and, thus, compose an interesting research topic. Computer modelling may yield insight into quadruplex folding and rearrangement, particularly molecular dynamics simulations. Here, we show that specific parameters, which are distinct from those commonly used in DNA conformational analyses, must be introduced for adequate interpretation and, most importantly, convenient visual representation of the quadruplex modelling results.

Nucleic Acids (Cont'd)

Introducing folding stability into the score function for computational design of RNA-binding peptides boosts the probability of success

Xingqing Xiao, Paul F. Agris and Carol K. Hall [North Carolina State University]

Proteins: Stru. Fun. & Bioinf., **84**, 700–711, 2016.

A computational strategy that integrates our peptide search algorithm with atomistic molecular dynamics simulation was used to design rational peptide drugs that recognize and bind to the anticodon stem and loop domain (ASL^{Lys3}) of human tRNA^{Lys3} for the purpose of interrupting HIV replication. The score function of the search algorithm was improved by adding a peptide stability term weighted by an adjustable factor λ to the peptide binding free energy.

Surfaces, Catalysts, and Materials Subjects

Adsorption of phenol molecules by sodium dodecyl sulfate (SDS) surfactants deposited on solid surfaces: A computer simulation study

Deneb Peredo-Mancilla, Hector Dominguez [Universidad Nacional Autónoma de México]

J. Mol.Graph. and Mod., **65**, 108-112, 2016.

Adsorption studies of phenol molecules on a sodium dodecyl sulfate (SDS) micelle were investigated by molecular dynamics simulations. Simulations were carried out in bulk and on three distinct solid surfaces, silicon dioxide, titanium dioxide and graphite. It was observed that different surfactant micellar shapes were formed on the surfaces. For the silicon dioxide and titanium dioxide surfaces the surfactants were adsorbed by their headgroups whereas for the graphite surface they were adsorbed mainly by their tail groups.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Improving quantitative structure–activity relationship models using Artificial Neural Networks trained with dropout

Jeffrey Mendenhall, Jens Meiler [Vanderbilt University]

J.Comp.Aided. Mol.des. **30**, 177-189, 2016.

Dropout is an Artificial Neural Network (ANN) training technique that has been shown to improve ANN performance across canonical machine learning (ML) datasets. Quantitative Structure Activity Relationship (QSAR) datasets used to relate chemical structure to biological activity in Ligand-Based Computer-Aided Drug Discovery pose unique challenges for ML techniques, such as heavily biased dataset composition, and relatively large number of descriptors relative to the number of actives. To test the hypothesis that dropout also improves QSAR ANNs, we conduct a benchmark on nine large QSAR datasets.

Potentials and Parameters

Evaluating thermodynamic integration performance of the new amber molecular dynamics package and assess potential halogen bonds of enoyl-ACP reductase (FabI) benzimidazole inhibitors

Pin-Chih Su and Michael E. Johnson [University of Illinois at Chicago]

J. Comp. Chem., **37**, 836–847, 2016.

Thermodynamic integration (TI) can provide accurate binding free energy insights in a lead optimization program, but its high computational expense has limited its usage. In the effort of developing an efficient and accurate TI protocol for FabI inhibitors lead optimization program, we carefully compared TI with different Amber molecular dynamics (MD) engines (sander and pmemd), MD simulation lengths, the number of intermediate states and transformation steps, and the Lennard-Jones and Coulomb Softcore potentials parameters in the one-step TI, using eleven benzimidazole inhibitors in complex with *Francisella tularensis* enoyl acyl reductase (FtFabI).

Additive CHARMM force field for naturally occurring modified ribonucleotides

You Xu, Kenno Vanommeslaeghe, Alexey Aleksandrov, Alexander D. MacKerell Jr. and Lennart Nilsson [Karolinska Institutet, HUDDINGE]

J. Comp. Chem., **37**, 896–912, 2016.

More than 100 naturally occurring modified nucleotides have been found in RNA molecules, in particular in tRNAs. We have determined molecular mechanics force field parameters compatible with the CHARMM36 all-atom additive force field for all these modifications using the CHARMM force field parametrization strategy. Emphasis was placed on fine tuning of the partial atomic charges and torsion angle parameters. The presented parameters will allow for computational studies of a wide range of RNAs containing modified nucleotides, including the ribosome and transfer RNAs.

Benchmarking Rapid TLES Simulations of Gas Diffusion in Proteins: Mapping O₂ Migration and Escape in Myoglobin as a Case Study

Maria S. Shadrina, Ann M. English, and Gilles H. Peslherbe [Concordia University]

J. Chem. Theor. and Comp, **12**, 2038–2046, 2016.

Standard MD simulations of gas diffusion consume considerable computational time and resources even for small proteins. To combat this, temperature-controlled locally enhanced sampling (TLES) examines multiple diffusion trajectories per simulation by accommodating multiple noninteracting copies of a gas molecule that diffuse independently, while the protein and water molecules experience an average interaction from all copies. Gas migration within a protein matrix can be accelerated without altering protein dynamics by increasing the effective temperature of the TLES copies.

Molecular Dynamics

Multiscale Simulations Reveal Key Aspects of the Proton Transport Mechanism in the ClC-ec1 Antiporter

Sangyun Lee, Jessica M.J. Swanson, Gregory A. Voth [The University of Chicago]

Biophysical Journal., **110**, 1334-1345, 2016.

Multiscale reactive MD simulations are used to study proton transport through the central region of ClC-ec1, a widely studied ClC transporter that enables the stoichiometric exchange of 2 Cl⁻ ions for 1 proton (H⁺). It has long been known that both Cl⁻ and proton transport occur through partially congruent pathways, and that their exchange is strictly coupled. However, the nature of this coupling and the mechanism of antiporting remain topics of debate. Here multiscale simulations have been used to characterize proton transport between E203 (Glu_{in}) and E148 (Glu_{ex}), the internal and external intermediate proton binding sites, respectively.

Molecular Dynamics (Cont'd)

Unraveling the mechanism of proton translocation in the extracellular half-channel of bacteriorhodopsin

Xiaoxia Ge [City College of New York] and M. R. Gunner

Proteins: Stru. Fun. & Bioinf., **84**, 639–654, 2016.

Bacteriorhodopsin, a light activated protein that creates a proton gradient in halobacteria, has long served as a simple model of proton pumps. Within bacteriorhodopsin, several key sites undergo protonation changes during the photocycle, moving protons from the higher pH cytoplasm to the lower pH extracellular side. To obtain a dynamic view of the key factors controlling proton translocation, a systematic study using molecular dynamics simulation was performed for eight bacteriorhodopsin models varying in retinal isomer and protonation states of the SB216, D85, D212, and E204.

The influence of Mg²⁺ coordination on ¹³C and ¹⁵N chemical shifts in CKI1_{RD} protein domain from experiment and molecular dynamics/density functional theory calculations

Jan Vícha, Martin Babinský, Gabriel Demo, Olga Otrusínová, Séverine Jansen, Blanka Pekárová, Lukáš Židek and Markéta L. Munzarová [Masaryk University]

Proteins: Stru. Fun. & Bioinf., **84**, 686–699, 2016.

Sequence dependence of ¹³C and ¹⁵N chemical shifts in the receiver domain of CKI1 protein from *Arabidopsis thaliana*, CKI1_{RD}, and its complexed form, CKI1_{RD}•Mg²⁺, was studied by means of MD/DFT calculations. MD simulations of a 20–ns production run length were performed. Nine explicitly hydrated structures of increasing complexity were explored, up to a 40-amino-acid structure. The size of the model necessary depended on the type of nucleus, the type of amino acid and its sequence neighbors, other spatially close amino acids, and the orientation of amino acid NH groups and their surface/interior position.

QM and QM/MM

Modeling emission features of salicylidene aniline molecular crystals: A QM/QM' approach

Davide Presti, Frédéric Labat, Alfonso Pedone, Michael J. Frisch, Hrant P. Hratchian, Ilaria Ciofini, Maria Cristina Menziani and Carlo Adamo [Institut de Recherche de Chimie Paris]

J. Comp. Chem., **37**, 861–870, 2016.

A new computational protocol relying on the use of electrostatic embedding, derived from QM/QM' ONIOM calculations, to simulate the effect of the crystalline environment on the emission spectra of molecular crystals is here applied to the β-form of salicylidene aniline (SA). The first singlet excited states (S₁) of the SA cis-keto and trans-keto conformers, surrounded by a cluster of other molecules representing the crystalline structure, were optimized by using a QM/QM' ONIOM approach with and without electronic embedding.

Combining classical molecular dynamics and quantum mechanical methods for the description of electronic excitations: The case of carotenoids

Ingrid G. Prandi, Lucas Viani, Oliviero Andreussi and Benedetta Mennucci [Dipartimento Di Chimica E Chimica Industriale]

J. Comp. Chem., **37**, 981–991, 2016.

Carotenoids are important actors both in light-harvesting (LH) and in photoprotection functions of photosynthetic pigment–protein complexes. A deep theoretical investigation of this multiple role is still missing owing to the difficulty of describing the delicate interplay between electronic and nuclear degrees of freedom. A possible strategy is to combine accurate quantum mechanical (QM) methods with classical molecular dynamics. To do this, however, accurate force–fields (FF) are necessary. This article presents a new FF for the different carotenoids present in LH complexes of plants.

QM and QM/MM (Cont'd)

DFT simulations and microkinetic modelling of 1-pentyne hydrogenation on Cu₂₀ model catalysts

Li Ma, Marko Melander, Timo Weckman, Saana Lipasti, Kari Laasonen, Jaakko Akola [Aalto University]

J. Mol. Graph. and Mod., **65**, 61-70, 2016.

Adsorption and dissociation of H₂ and hydrogenation of 1-pentyne on neutral and anionic Cu₂₀ clusters have been investigated using the density functional theory and microkinetic modelling. Molecular adsorption of H₂ is found to occur strictly at atop sites. The H₂ dimer is activated upon adsorption, and the dissociation occurs with moderate energy barriers. The dissociated H atoms reside preferentially on 3-fold face and 2-fold edge sites. Based on these results, the reaction paths leading to the partial and total hydrogenation of 1-pentyne have been studied step-by-step.

Comparison of Methods To Reweight from Classical Molecular Simulations to QM/MM Potentials

Eric C. Dybeck, Gerhard König, Bernard R. Brooks, and Michael R. Shirts [University of Virginia, Charlottesville]

J. Chem. Theor. and Comp., **12**, 1466–1480, 2016.

We examine methods to reweight classical molecular mechanics solvation calculations to more expensive QM/MM energy functions. We first consider the solvation free energy difference between ethane and methanol in a QM/MM Hamiltonian from configurations generated in a cheaper MM potential. The solute molecules in the QM/MM Hamiltonian are treated with B3LYP/6-31G*, and the solvent water molecules are treated classically. The free energy difference in the QM/MM Hamiltonian is estimated using Boltzmann reweighting with both the non-Boltzmann Bennett method (NBB) and the multistate Bennett acceptance ratio (MBAR), and the variance of each method is directly compared for an identical data set.

Derivation of Reliable Geometries in QM Calculations of DNA Structures: Explicit Solvent QM/MM and Restrained Implicit Solvent QM Optimizations of G-Quadruplexes

Konstantinos Gkionis, Holger Kruse, and Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp., **12**, 2000–2016, 2016.

Modern dispersion-corrected DFT methods have made it possible to perform reliable QM studies on complete nucleic acid (NA) building blocks having hundreds of atoms. Such calculations, although still limited to investigations of potential energy surfaces, enhance the portfolio of computational methods applicable to NAs and offer considerably more accurate intrinsic descriptions of NAs than standard MM. Here we compare two approaches designed to suppress such artifacts: partially restrained continuum solvent QM and explicit solvent QM/MM optimizations. We report geometry relaxations of a set of diverse double-quartet guanine quadruplex (GQ) DNA stems. Both methods provide neat structures without major artifacts.

QM and QM/MM (Cont'd)

Catalytic Mechanism of Nitrile Hydratase Subsequent to Cyclic Intermediate Formation: A QM/MM Study

Megumi Kayanuma [University of Tsukuba], Mitsuo Shoji, Masafumi Yohda, Masafumi Odaka, and Yasuteru Shigeta

J. Phys. Chem. B., **120**, 3259–3266, 2016.

The catalytic mechanism of an Fe-containing nitrile hydratase (NHase) subsequent to the formation of a cyclic intermediate was investigated using a hybrid quantum mechanics/molecular mechanics (QM/MM) method. We identified the following mechanism: (i) proton transfer from β Tyr72 to the substrate via α Ser113, and cleavage of the S–O bond of α Cys114–SO[−] and formation of a disulfide bond between α Cys109 and α Cys114; (ii) direct attack of a water molecule on the sulfur atom of α Cys114, which resulted in the generation of both an imidic acid and a renewed sulfenic cysteine; and (iii) isomerization of the imidic acid to the amide.

Photophysics of the LOV-Based Fluorescent Protein Variant iLOV-Q489K Determined by Simulation and Experiment

Mehdi D. Davari, Benita Kopka, Marcus Wingen, Marco Bocola, Thomas Drepper, Karl-Erich Jaeger, Ulrich Schwaneberg, and Ulrich Krauss [Heinrich Heine University Düsseldorf]

J. Phys. Chem. B., **120**, 3344–3352, 2016.

Light, oxygen, voltage (LOV) based fluorescent proteins (FPs) represent a promising alternative to fluorescent reporters of the green fluorescent protein family. For certain applications like multicolor imaging or the design of FRET-based biosensors, the generation of spectrally shifted LOV-based FPs would be required. Here, we describe the experimental characterization of this variant, which, surprisingly contrary to the theoretical prediction, shows blue-shifted absorption and fluorescence-emission maxima.

Ligand Docking

A Role for Weak Electrostatic Interactions in Peripheral Membrane Protein Binding

Hanif M. Khan, Tao He, Edvin Fuglebakk, Cédric Grauffel, Boqian Yang, Mary F. Roberts, Anne Gershenson, Nathalie Reuter [University of Bergen]

Biophysical Journal., **110**, 1367–1378, 2016.

Bacillus thuringiensis phosphatidylinositol-specific phospholipase C (BtPI-PLC) is a secreted virulence factor that binds specifically to phosphatidylcholine (PC) bilayers containing negatively charged phospholipids. BtPI-PLC carries a negative net charge and its interfacial binding site has no obvious cluster of basic residues. Comparisons of molecular-dynamics simulations performed using different lipid compositions reveal that the bilayer composition does not affect either hydrogen bonds or hydrophobic contacts between the protein interfacial binding site and bilayers.

Toward the identification of molecular cogs

Maciej Dziubiński and Bogdan Lesyng [University of Warsaw]

J. Comp. Chem., **37**, 848–860, 2016.

Computer simulations of molecular systems allow determination of microscopic interactions between individual atoms or groups of atoms, as well as studies of intramolecular motions. Nevertheless, description of structural transformations at the mesoscopic level and identification of causal relations associated with these transformations is very difficult. Structural and functional properties are related to free energy changes. The method presented in this work quantifies the energetic contribution of each pair of atoms to the total free energy change along a given collective variable.

Ligand Docking (Cont'd)

Novel binding patterns between ganoderic acids and neuraminidase: Insights from docking, molecular dynamics and MM/PBSA studies

Zhiwei Yang, Fei Wu, Xiaohui Yuan, Lei Zhang, Shengli Zhang [Xi'an Jiaotong University]

J. Mol. Graph. and Mod., **65**, 27-34, 2016.

Recently, ganoderic acids (GAs) give rise to the attractive candidates of novel neuraminidase (NA) inhibitors. However, there is still no evident conclusion about their binding patterns. To this end, docking, molecular dynamics and MM/PBSA methods were combined to study the binding profiles of GAs with the N1 protein and familiar H274Y and N294S mutations (A/Vietnam/1203/04 stain). It was found that the binding affinities of ganoderic acid DM and Z (ΔG_{bind} , -16.83 and -10.99 kcal mol $^{-1}$) are comparable to that of current commercial drug oseltamivir (-23.62 kcal mol $^{-1}$).

Mechanistic Study of Human Glucose Transport Mediated by GLUT1

Xuegang Fu, Gang Zhang, Ran Liu, Jing Wei, Daisy Zhang-Negrerie, Xiaodong Jian, and Qingzhi Gao [Tianjin University]

J. Chem. Infor. and Mod., **56**, 517–526, 2016.

The glucose transporter 1 (GLUT1) belongs to the major facilitator superfamily (MFS) and is responsible for the constant uptake of glucose. However, the molecular mechanism of sugar transport remains obscure. In this study, homology modeling and molecular dynamics (MD) simulations in lipid bilayers were performed to investigate the combination of the alternate and multisite transport mechanism of glucose with GLUT1 in atomic detail. To explore the substrate recognition mechanism, the outward-open state human GLUT1 homology model was generated based on the template of xylose transporter XylE (PDB ID: [4GBZ](#)), which shares up to 29% sequence identity and 49% similarity with GLUT1.

Three-Dimensional Similarity in Molecular Docking: Prioritizing Ligand Poses on the Basis of Experimental Binding Modes

Andrew Anighoro and Jürgen Bajorath [Rheinische Friedrich-Wilhelms-Universität]

J. Chem. Infor. and Mod., **56**, 580–587, 2016.

Molecular docking is the premier approach to structure-based virtual screening. While ligand posing is often successful, compound ranking using force field-based scoring functions remains difficult. Uncertainties associated with scoring often limit the ability to confidently identify new active compounds. In this study, we introduce an alternative approach to compound ranking. Rather than using scoring functions for final ranking, compounds are prioritized on the basis of computed 3D similarity to known crystallographic ligands.

Mechanism and rate constants of the Cdc42 GTPase binding with intrinsically disordered effectors

Xiaodong Pang and Huan-Xiang Zhou [Department of Physics and Institute of Molecular Biophysics, Tallahassee]

Proteins: Stru. Fun. & Bioinf., **84**, 674–685, 2016.

Intrinsically disordered proteins (IDPs) are often involved in signaling and regulatory functions, through binding to cellular targets. Many IDPs undergo disorder-to-order transitions upon binding. Both the binding mechanisms and the magnitudes of the binding rate constants can have functional importance. We applied our TransComp method within the framework of the dock-and-coalesce mechanism to dissect the binding kinetics of two Rho-family GTPases, Cdc42 and TC10, with two intrinsically disordered effectors, WASP and Pak1.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 65, April, 2016.

- 1-7 **Why do the outer membrane proteins OmpF from *E. coli* and OprP from *P. aeruginosa* prefer trimers? Simulation studies**, Jitti Niramitranon, Mark SP Sansom, Prapasiri Pongprayoon [Kasetsart University]

See Applications / Protein Confirmation Analysis.

- 8-14 **Conformational changes of A β (1–42) monomers in different solvents**, Myeongsang Lee, Hyun Joon Chang, Jung Yeon Park, Joonha Shin, Jong Woo Park, Jee Woo Choi, Jae In Kim, Sungsoo Na [Korea University]

See Applications / Protein Confirmation Analysis.

- 15-26 **Computational studies on receptor–ligand interactions between novel buffalo (*Bubalus bubalis*) nucleotide-binding oligomerization domain-containing protein 2 (NOD2) variants and muramyl dipeptide (MDP)**, Biswajit Brahma, Mahesh Chandra Patra, Purusottam Mishra, Bidhan Chandra De, Sushil Kumar, Jitendra Maharana, Ashutosh Vats, Sonika Ahlawat, Tirtha Kumar Datta, Sachinandan De [National Dairy Research Institute, Karnal]

See Applications / Ligand Binding.

- 27-34 **Novel binding patterns between ganoderic acids and neuraminidase: Insights from docking, molecular dynamics and MM/PBSA studies**, Zhiwei Yang, Fei Wu, Xiaohui Yuan, Lei Zhang, Shengli Zhang [Xi'an Jiaotong University]

See Methodology / Ligand Docking.

- 35-42 **Tetrel bonds between PySiX₃ and some nitrogenated bases: Hybridization, substitution, and cooperativity**, Mingxiu Liu, Qingzhong Li [Yantai University], Wenzuo Li, Jianbo Cheng

Ab initio calculations have been performed to study the influence of hybridization, substitution, and cooperativity on the tetrel bond in the complexes of PySiX₃ (Py = pyridine and X = halogen).

- 43-60 **Development of an accurate molecular mechanics model for buckling behavior of multi-walled carbon nanotubes under axial compression**, B. Safaei [Islamic Azad University], P. Naseradinmousavi, A. Rahmani

In the present paper, an analytical solution based on a molecular mechanics model is developed to evaluate the elastic critical axial buckling strain of chiral multi-walled carbon nanotubes (MWCNTs). To this end, the total potential energy of the system is calculated with the consideration of the both bond stretching and bond angular variations.

- 61-70 **DFT simulations and microkinetic modelling of 1-pentyne hydrogenation on Cu₂₀ model catalysts**, Li Ma, Marko Melander, Timo Weckman, Saana Lipasti, Kari Laasonen, Jaakko Akola [Aalto University]

See Methodology / QM and QM/MM.

- 71-82 **New design of nucleotide excision repair (NER) inhibitors for combination cancer therapy**, Francesco Gentile, Jack A. Tuszynski, Khaled H. Barakat [University of Alberta]

Many cancer chemotherapy agents act by targeting the DNA of cancer cells, causing substantial damage within their genome and causing them to undergo apoptosis. An effective DNA repair pathway in cancer cells can act in a reverse way by removing these drug-induced DNA lesions, allowing cancer cells to survive, grow and proliferate. Here, we build upon our recent advances in identifying inhibitors for this interaction and continue our efforts to rationally design more effective and potent regulators for the NER pathway.

- 83-93 **Theoretical study of chlordecone and surface groups interaction in an activated carbon model under acidic and neutral conditions**, Juan José Gamboa-Carballo, Kenia Melchor-Rodríguez, Daniel Hernández-Valdés, Carlos Enriquez-Victorero, Ana Lilian Montero-Alejo, Sarra Gaspard, Ulises Javier Jáuregui-Haza [Instituto Superior de Tecnologías y Ciencias Aplicadas]

Activated carbons (ACs) are widely used in the purification of drinking water without almost any knowledge about the adsorption mechanisms of the persistent organic pollutants. Chlordecone (CLD, Kepone) is an organochlorinated synthetic compound that has been used mainly as agricultural insecticide.

- 94-99 **iBET: Immersive visualization of biological electron-transfer dynamics**, C. Masato Nakano, Erick Moen, Hye Suk Byun, Heng Ma, Bradley Newman, Alexander McDowell, Tao Wei, Mohamed Y. El-Naggar [University of Southern California]

See Applications / Bioinformatics.

- 100-107 **Docking and ADMET prediction of few GSK-3 inhibitors divulges 6-bromoindirubin-3-oxime as a potential inhibitor**, Chaluveelaveedu Murleedharan Nisha, Ashwini Kumar, Archana Vimal, Bhukya Mounika Bai, Dharm Pal, Awanish Kumar [National Institute of Technology, Raipur]

See Applications / Medicinal Chemistry and Drug Design.

- 108-112 **Adsorption of phenol molecules by sodium dodecyl sulfate (SDS) surfactants deposited on solid surfaces: A computer simulation study**, Deneb Peredo-Mancilla, Hector Dominguez [Universidad Nacional Autónoma de México]

See Applications / Surfaces, Catalysts and Material subjects.

- 113-128 **Exploring isoxazole and carboxamide derivatives as potential non-nucleoside reverse transcriptase inhibitors**, Sudheer S. Kurup, Kaustubh A. Joshi [Institute of Chemical Technology, Nathalal Parekh Marg]

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 37 (9), April, 2016.

- 787–794 **Surface chemistry of oxygen on aluminum—Performance of the density functionals: PBE, PBE0, M06, and M06-L**, Cláudio M. Lousada [KTH Royal Institute of Technology] and Pavel A. Korzhavyi

We investigated the performance of the density functional theory (DFT) functionals PBE, PBE0, M06, and M06-L for describing the molecular and dissociative adsorption of O₂ onto pure and doped Al(111) surfaces.

- 795–804 **A new algorithm for construction of coarse-grained sites of large biomolecules**, Min Li, John Z. H. Zhang and Fei Xia [NYU-ECNU Center for Computational Chemistry at NYU Shanghai]

See Applications / General and Model Systems.

- 805–812 **Real-time feedback from iterative electronic structure calculations**, Alain C. Vaucher, Moritz P. Haag and Markus Reiher [ETH Zürich]

Real-time feedback from iterative electronic structure calculations requires to mediate between the inherently unpredictable execution times of the iterative algorithm used and the necessity to provide data in fixed and short time intervals for real-time rendering. We introduce the concept of a mediator as a component able to deal with infrequent and unpredictable reference data to generate reliable feedback.

- 813–824 **How the substituents in corannulene and sumanene derivatives alter their molecular assemblings and charge transport properties?—A theoretical study with a dimer model**, Xi Chen, Fu-Quan Bai, Yongang Tang and Hong-Xing Zhang [Jilin University]

The substituent effects on the structures, intermolecular interactions and charge transport properties of a series of corannulene and sumanene derivatives were investigated by DFT method. The intermolecular interaction energy and the potential energy surface of the dimers were also calculated and analyzed in detail, which showed several local energy minima and demonstrated the possible dimer structures in experiment.

- 825–835 **4f fine-structure levels as the dominant error in the electronic structures of binary lanthanide oxide**, Bolong Huang [City University of Hong Kong]

The ground-state 4f fine-structure levels in the intrinsic optical transition gaps between the 2p and 5d orbitals of lanthanide sesquioxides (Ln₂O₃, Ln = La...Lu) were calculated by a two-way crossover search for the U parameters for DFT + U calculations.

- 836–847 **Evaluating thermodynamic integration performance of the new amber molecular dynamics package and assess potential halogen bonds of enoyl-ACP reductase (FabI) benzimidazole inhibitors**, Pin-Chih Su and Michael E. Johnson [University of Illinois at Chicago]

See Methodology / Potentials and Parameters.

- 848–860 **Toward the identification of molecular cogs**, Maciej Dziubiński and Bogdan Lesyng [University of Warsaw]

See Methodology / Ligand Docking.

- 861–870 **Modeling emission features of salicylidene aniline molecular crystals: A QM/QM' approach**, Davide Presti, Frédéric Labat, Alfonso Pedone, Michael J. Frisch, Hrant P. Hratchian, Ilaria Ciofini, Maria Cristina Menziani and Carlo Adamo [Institut de Recherche de Chimie Paris]

See Methodology / QM and QM/MM.

Journal of Computational Chemistry, 37 (10), April, 2016.

- 877–885 **The hydration properties of carboxybetaine zwitterion brushes**, Hongbo Du and Xianghong Qian [University of Arkansas]

Combined quantum mechanical calculations and classical molecular dynamics simulations were conducted to investigate the hydration properties of carboxybetaine zwitterion brushes with varying separation distances between the quaternary ammonium cation and carboxylic anion.

- 886–895 **Possible mechanism of BN fullerene formation from a boron cluster: Density-functional tight-binding molecular dynamics simulations**, Y. Ohta [Nara Women's University]

We simulate the formation of a BN fullerene from an amorphous B cluster at 2000 K by quantum mechanical molecular dynamics based on the density-functional tight-binding method. We run 30 trajectories 200 ps in length, where N atoms are supplied around the target cluster, which is initially an amorphous B₃₆ cluster. Most of the incident N atoms are promptly incorporated into the target cluster to form B-N-B bridges or NB₃ pyramidal local substructures.

- 896–912 **Additive CHARMM force field for naturally occurring modified ribonucleotides**, You Xu, Kenno Vanommeslaeghe, Alexey Aleksandrov, Alexander D. MacKerell Jr. and Lennart Nilsson [Karolinska Institutet, HUDDINGE]

See Methodology / Potentials and Parameters.

- 913–919 **The role of protein “Stability patches” in molecular recognition: A case study of the human growth hormone-receptor complex**, Roman Osman, Mihaly Mezei and Stanislav Engel [Ben-Gurion University of the Negev]

See Applications / Protein-Protein Interactions.

- 920–926 **Implicit solvent coarse-grained model of polyamidoamine dendrimers: Role of generation and pH**, Leebyn Chong, Fikret Aydin and Meenakshi Dutt [Rutgers the State University of New Jersey]

See Applications / Protein Dynamics.

- 927–939 **Parallelization and improvements of the generalized born model with a simple sWitching function for modern graphics processors**, Evan J. Arthur and Charles L. Brooks III [University of Michigan]

Two fundamental challenges of simulating biologically relevant systems are the rapid calculation of the energy of solvation and the trajectory length of a given simulation. The Generalized Born model with a Simple sWitching function (GBSW) addresses these issues by using an efficient approximation of Poisson–Boltzmann (PB) theory to calculate each solute atom's free energy of solvation, the gradient of this potential, and the subsequent forces of solvation without the need for explicit solvent molecules.

- 940–946 **A mixed DFT-MD methodology for the in silico development of drug releasing macrocycles. Calix and thia-calix[N]arenes as carriers for Bosutinib and Sorafenib**, Rodrigo Galindo-Murillo, Luis Enrique Aguilar-Suárez and Joaquín Barroso-Flores [Centro Conjunto De Investigación En Química Sustentable UAEM-UNAM]

See Applications / Medicinal Chemistry and Drug Design.

- 947–953 **On the zeroth-order hamiltonian for CASPT2 calculations of spin crossover compounds**, Sergi Vela [Université de Strasbourg], Maria Fumanal, Jordi Ribas-Ariño and Vincent Robert

Complete active space self-consistent field theory (CASSCF) calculations and subsequent second-order perturbation theory treatment (CASPT2) are discussed in the evaluation of the spin-states energy difference (ΔH_{elec}) of a series of seven spin crossover (SCO) compounds. The reference values have been extracted from a combination of experimental measurements and DFT + U calculations, as discussed in a recent article (Vela et al., Phys Chem Chem Phys 2015, 17, 16306).

Journal of Computational Chemistry, 37 (11), April, 2016.

- 961–970 **Focused grid-based resampling for protein docking and mapping**, Artem B. Mamonov, Mohammad Moghadasi, Hanieh Mirzaei, Shahrooz Zarbafian, Laurie E. Grove, Tanggis Bohnuud, Pirooz Vakili, Ioannis Ch. Paschalidis, Sandor Vajda and Dima Kozakov [Stony Brook University]

See Applications / Protein-Protein Interactions.

- 971–975 **Effects of an electric field on interaction of aromatic systems**, Il Seung Youn, Woo Jong Cho [Ulsan National Institute of Science and Technology] and Kwang S. Kim

The effect of uniform external electric field on the interactions between small aromatic compounds and an argon atom is investigated using post-HF (MP2, SCS-MP2, and CCSD(T)) and density functional (PBE0-D3, PBE0-TS, and vdW-DF2) methods.

- 976–980 **Effective protein conformational sampling based on predicted torsion angles**, Yuedong Yang and Yaoqi Zhou [Griffith University]

See Applications / Protein Conformational Analysis.

- 981–991 **Combining classical molecular dynamics and quantum mechanical methods for the description of electronic excitations: The case of carotenoids**, Ingrid G. Prandi, Lucas Viani, Oliviero Andreussi and Benedetta Mennucci [Dipartimento Di Chimica E Chimica Industriale]

See Methodology / QM and QM/MM.

- 992–1004 **Structures and energetics of complexation of metal ions with ammonia, water, and benzene: A computational study**, Bhaskar Sharma, Y. Indra Neela and G. Narahari Sastry [CSIR-Indian Institute of Chemical Technology]

Quantum chemical calculations have been performed at CCSD(T)/def2-TZVP level to investigate the strength and nature of interactions of ammonia (NH₃), water (H₂O), and benzene (C₆H₆) with various metal ions and validated with the available experimental results.

- 1005–1018 **Density functional theory of the Cu_A-like Cu₂S₂ diamond core in Cu 2H(NGuaS)₂Cl₂**, M. Witte [Universität Paderborn], U. Gerstmann, A. Neuba, G. Henkel and W. G. Schmidt

Density functional theory (DFT) calculations with localized as well as plane-wave basis functions are performed for the recently reported dicopper thiolate species Cu₂(NGuaS)₂Cl₂ [NGuaS = 2-(1,1,3,3-tetramethylguanidino) benzenethiolate, C₁₁H₁₆N₃S] and its bromo derivative [Neuba et al., Angew. Chem. Int. Ed. 2012, 51, 1714.].

Journal of Molecular Modeling, 22 (4), April, 2016.

- 100 **A DFT investigation on the structural and antioxidant properties of new isolated interglycosidic O-(1 → 3) linkage flavonols**, Gabriel L. C. de Souza [Universidade Federal de Mato Grosso], Leonardo M. F. de Oliveira, Rafael G. Vicari, Alex Brown

We present a computational study on two flavonols that were recently isolated from Loranthaceae family plant extracts: kaempferol 3-O- α -L-arabinofuranosyl-(1 → 3)- α -L-rhamnoside and quercetin 3-O- α -L-arabinofuranosyl-(1 → 3)- α -L-rhamnoside.

- 99 **Melt-phase behavior of collapsed PMMA/PVC chains revealed by multiscale simulations**, Chaofu Wu [Hunan University of Humanities Science & Technology]

Single- and double-chain models of three stereoregular polymers, iso- and syndiotactic poly(methyl methacrylate) and isotactic poly(vinyl chloride), were extensively simulated using systematic coarse-grained (CG) potentials.

- 98 **Mapping the intrinsically disordered properties of the flexible loop domain of Bcl-2: a molecular dynamics simulation study**, Ian Ilizaliturri-Flores, José Correa-Basurto, Martiniano Bello, Jorge L. Rosas-Trigueros, Beatriz Zamora-López, Claudia G. Benítez-Cardoza, Absalom Zamorano-Carrillo [Ciudad de México]

See Applications / Protein Confirmation Analysis.

- 97 **A theoretical prediction of the relationships between the impact sensitivity and electrostatic potential in strained cyclic explosive and application to H-bonded complex of nitrocyclohydrocarbon**, Fu-de Ren [North University of China], Duan-lin Cao, Wen-jing Shi, Hong-fei Gao

Seven models that related the features of molecular surface electrostatic potentials (ESPs) above the bond midpoints and rings, statistical parameters of ESPs to the experimental impact sensitivities h_{50} of eight

strained cyclic explosives with the C–NO₂ bonds were theoretically predicted at the DFT-B3LYP/6-311++G** level.

- 96 **A dynamics prediction of nitromethane → methyl nitrite isomerization in external electric field**, Fu-de Ren [North University of China], Duan-lin Cao, Wen-jing Shi

As a follow-up to our investigation into the effect of external electric field on the chemical bond strength, the effects of external electric field on the CH₃NO₂ → CH₃ONO isomerization dynamics were investigated using the MP2/6-311++G(2d,p) and CCSD/6-311++G(2d,p) methods.

- 95 **A theoretical study on the hydrogen-bonding interactions between flavonoids and ethanol/water**, Yan-Zhen Zheng, Yu Zhou, Qin Liang, Da-Fu Chen [Fujian Agriculture and Forestry University], Rui Guo

Ethanol and water are the solvents most commonly used to extract flavonoids from propolis. Do hydrogen-bonding interactions exist between flavonoids and ethanol/water? In this work, this question was addressed by using density functional theory (DFT) to provide information on the hydrogen-bonding interactions between flavonoids and ethanol/water. Chrysin and Galangin were chosen as the representative flavonoids.

- 94 **The mechanisms for N-heterocyclic olefin-catalyzed formation of cyclic carbonate from CO₂ and propargylic alcohols**, Zhi-E Yan, Rui-Ping Huo, Li-hui Guo, Xiang Zhang [Shanxi Normal University]

The mechanistic details of N-heterocyclic olefin-catalyzed formation of cyclic carbonate from CO₂ and propargylic alcohols were investigated by DFT calculations. Six mechanisms, four for the formation of five-membered cyclic carbonate (**M-A**, **M-B**, **M-B'** and **M-C**), and two for six-membered cyclic carbonate (**M-D** and **M-E**), were fully investigated.

- 93 **KRAKENX: software for the generation of alignment-independent 3D descriptors**, Vishwesh Venkatraman, Bjørn Kåre Alsberg [Norwegian University of Science and Technology]

See Applications / Bioinformatics.

- 92 **Investigation of the effect of erythrosine B on amyloid beta peptide using molecular modeling**, Juho Lee, Inchon Kwon, Seung Soon Jang, Art E. Cho [Korea University, Sejong]

See Applications / Medicinal Chemistry and Drug Design.

- 91 **Impacts of the charged residues mutation S48E/N62H on the thermostability and unfolding behavior of cold shock protein: insights from molecular dynamics simulation with Gō model**, Ji-Guo Su, Xiao-Ming Han, Shu-Xin Zhao, Yan-Xue Hou, Xing-Yuan Li, Li-Sheng Qi, Ji-Hua Wang [Dezhou University]

See Applications / Protein Dynamics.

- 90 **Homology modeling, docking, and molecular dynamics simulation of the receptor GALR2 and its interactions with galanin and a positive allosteric modulator**, Wen-Qi Hui, Qi Cheng, Tian-Yu Liu, Qin Ouyang [Third Military Medical University]

See Applications / Ligand Binding.

- 89 **Structural Insight for Roles of DR5 Death Domain Mutations on Oligomerization of DR5 Death Domain–FADD Complex in the Death-Inducing Signaling Complex Formation: A Computational Study**, Hongyi Yang, Yuhua Song [The University of Alabama at Birmingham]

See Applications / Protein Confirmation Analysis.

- 88 **Density functional study of H₂O molecule adsorption on α -U(001) surface**, Shansong Huang [Nanjing University of Science and Technology], Xiu-Lin Zeng, Feng-Qi Zhao, Xuehai Ju

Periodic density functional theory (DFT) calculations were performed to investigate the adsorption of H₂O on U(001) surface. The metallic nature of uranium atom and different adsorption sites of U(001) surface play key roles in the H₂O molecular dissociate reaction.

- 87 **Attaching an alkali metal atom to an alkaline earth metal oxide (BeO, MgO, or CaO) yields a triatomic metal oxide with reduced ionization potential and redirected polarity**, Grzegorz Nowiak, Piotr Skurski, Iwona Anusiewicz [University of Gdańsk]

The existence of a series of neutral triatomic metal oxides MON and their corresponding cations MON⁺ (M = Be, Mg, Ca; N = Li, Na, K) was postulated and verified theoretically using ab initio methods at the CCSD(T)/6-311+G(3df)//MP2/6-311+G(3df) level of theory.

- 86 **Stereochemistry and spectroscopic analysis of bis-Betti base derivatives of 2,3-dihydroxynaphthalene**, Mehdi Zamani [Damghan University], Mehdi Shafiee, Mohammad Hossein Keshavarz

Density functional theory (DFT) was used to study the stereochemistry, thermodynamic stability, and spectra of recently synthesized bis-Betti base derivatives of 2,3-dihydroxynaphthalene obtained through multicomponent reactions of 2,3-dihydroxynaphthalene with aminoisoxazole and benzaldehyde derivatives.

- 85 **How strong is the edge effect in the adsorption of anticancer drugs on a graphene cluster?**, Chompoonut Rungnim, Rungroj Chanajaree, Thanyada Rungrotmongkol, Supot Hannongbua, Nawee Kungwan, Peter Wolschann, Alfred Karpfen, Vudhichai Parasuk [Chulalongkorn University]

The adsorption of nucleobase-analog anticancer drugs (fluorouracil, thioguanine, and mercaptopurine) on a graphene flake (C₅₄H₁₈) was investigated by shifting the site at which adsorption occurs from one end of the sheet to the other end.

- 84 **Solvent effect on molecular structure, IR spectra, thermodynamic properties and chemical stability of zoledronic acid: DFT study**, Qingzhu Liu, Ling Qiu, Yang Wang, Gaochao Lv, Guiqing Liu, Shanshan Wang, Jianguo Lin [Jiangsu Institute of Nuclear Medicine]

Zoledronic acid (ZL) has been used widely for treating skeletal diseases because of its high potency in inhibiting bone resorption. A detailed understanding of its physicochemical characteristics may be of great significance in both medicinal chemistry and structural biology for the design of novel bisphosphonates with higher activity. In the present work, the monoclinic (IM) and triclinic (IT) polymorphs of ZL in the gas phase and the aqueous phase were studied by density functional theory (DFT) method at the B3LYP/6-311++G** level.

- 83 **Theoretical study of the effect of N-oxides on the performances of energetic compounds**, Wei-peng Lai [Xi'an Modern Chemistry Research Institute], Peng Lian, Zhong-xue Ge, Ying-zhe Liu, Tao Yu, Jian Lv

In order to study the effects of N-oxide on structure and performance, six categories of energetic compounds were systemically investigated. The results indicated that the C–C bonds in the rings were shortened, and the C–N bonds close to the N → O bond were elongated when N atoms was oxidized to form N → O bonds. N → O bonds can increase the densities of most categories of compounds, and the increment will increase with the number of N → O bonds.

- 82 **Molecular dynamics simulations of trihalomethanes removal from water using boron nitride nanosheets**, Jafar Azamat, Alireza Khataee, Sang Woo Joo [Yeungnam University]

Molecular dynamics simulations were performed to investigate the separation of trihalomethanes (THMs) from water using boron nitride nanosheets (BNNSs). The studied systems included THM molecules and a functionalized BNNS membrane immersed in an aqueous solution.

- 81 **Theoretical insights into thermal cyclophanediene to dihydropyrene electrocyclic reactions; a comparative study of Woodward Hoffmann allowed and forbidden reactions**, Bibi Saima, Afsar Khan, Riffat Un Nisa, Tariq Mahmood, Khurshid Ayub[COMSATS Institute of Information Technology]

The thermally allowed electrocyclic reaction syn-cyclophanediene (CPD) to dihydropyrene (DHP) was compared with the disallowed thermal electrocyclic reaction in anti CPD through density functional theory (DFT) calculations at the B3LYP/6-31 + G(d) level.

- 80 **Molecular modeling of zinc paddlewheel molecular complexes and the pores of a flexible metal organic framework**, Khalid A. H. Alzahrani, Robert J. Deeth [University of Warwick]

A new all-atom first-principles force field (FF) is constructed for the bimetallic, four-bladed zinc paddlewheel (ZPW) motif. Zinc-ligand interactions are described via Morse functions and the angular geometry at the metal centers is modeled with a pure ligand-ligand repulsion term.

- 79 **Methane activation on nickel oxide clusters with a concerted mechanism: a density functional theory study of the effect of silica support**, Yanyan Xi, Bili Chen, Xufeng Lin [China University of Petroleum (East China)], Chuangye Wang, Hui Fu

The support effect is an important issue in heterogeneous catalysis. A systematic density functional theory (DFT) study was performed to investigate the support effect of a silica model on the initial step of methane activation on Ni_xO_x (x = 2, 3) clusters with a concerted mechanism.

- 78 **Theoretical prediction of complexes with a sulfur–carbon triple bond: SCX²⁺, SCXF⁺, and SCXF₂ (X = Be, Mg, Ca)**, Chen Guo [Northeast Agricultural University, Harbin], Na Hou, Chong Wang

A new series of compounds with a sulfur–carbon triple bond—SCX²⁺, SCXF⁺, and SCXF₂ (X = Be, Mg, Ca)—were investigated using quantum chemical computations. The B3LYP, M06-2X, MP2, CCSD, and G4 methods were employed to predict the structures, harmonic vibrational frequencies, Wiberg bond indices, and adiabatic bond dissociation energies (ABDEs) for these compounds.

- 77 **Hydrogen bonded and stacked geometries of the temozolomide dimer**, Okuma Emile Kasende, Jules Tshishimbi Muya, Vincent de Paul N. Nziko, Steve Scheiner [Utah State University, Logan]

Dispersion-corrected density functional theory (DFT) and MP2 quantum chemical methods are used to examine homodimers of temozolomide (TMZ). Of the 12 dimer configurations found to be minima, the antarafacial stacked dimer is the most favored, it is lower in energy than coplanar dimers which are stabilized by H-bonds.

- 76 **Evaluation of modern DFT functionals and G3n-RAD composite methods in the modelization of organic singlet diradicals**, Diego López-Carballeira, Fernando Ruipérez [University of the Basque Country UPV/EHU]

The evaluation of four high-level composite methods based on the modification of Gaussian-3 (G3) theory for radicals and 18 exchange-correlation density functionals, including modern long-range and dispersion-corrected functionals, in the modelization of singlet diradicals has been performed in this work.

- 75 **Predictive analysis of chitosan-based nanocomposite biopolymers elastic properties at nano- and microscale**, Elena L. Kossovich [National University of Science and Technology "MISiS", 4], Roman A. Safonov

Chitosan nanocomposites mechanical properties play a major role in usage of such materials for specific areas of application, mostly in medicine and development of ecologically-friendly production. Computer-based predictive modelling of such composites will reduce costs of their development. In this paper, a multiscale approach for structural characterization and evaluation of mechanical properties is proposed based on hybrid coarse-grained/all atom molecular dynamics.

- 74 **Free energy calculation provides insight into the action mechanism of selective PARP-1 inhibitor**, Ran Cao [Peking Union Medical College]

See Applications / Medicinal Chemistry and Drug Design.

- 73 **The impact of position and number of methoxy group(s) to tune the nonlinear optical properties of chalcone derivatives: a dual substitution strategy**, Shabbir Muhammad [King Khalid University], Abdullah G. Al-Sehemi, Ahmad Irfan, Aijaz R. Chaudhry, Hamid Gharni, S. AlFaify, Mohd Shkir, Abdullah M. Asiri

Using the state-of-art computational techniques, we limelight a structure–property relationship for the position and number of methoxy group(s) to tune the optical and nonlinear optical (NLO) properties (first hyperpolarizability) of chalcone derivatives.

- 72 **PDP-CON: prediction of domain/linker residues in protein sequences using a consensus approach**, Piyali Chatterjee, Subhadip Basu [Jadavpur University], Julian Zubek, Mahantapas Kundu, Mita Nasipuri, Dariusz Plewczynski

See Applications / Protein Structure Analysis.

- 71 **Modeling of babesipain-1 and identification of natural and synthetic leads for bovine babesiosis drug development**, Potshangbam Angamba Meetei, R. S. Rathore, N. Prakash Prabhu, Vaibhav Vindal [University of Hyderabad]

Babesiosis is a tick-borne, zoonotic disease caused by species of the intraerythrocytic protozoan *Babesia*. It is distributed all around the world and affects various domestic and wild animals, mainly cattle. Recently, the

cysteine protease enzyme, babesipain-1 from *Babesia bigemina* has been identified as a potential target for designing new anti-babesiosis drugs. In the present study, a three-dimensional structural model of babesipain-1 was developed.

- 70 **N–H bond cleavage of ammonia on graphene-like B₃₆ borophene: DFT studies**, Zahra Rostami [Payame Noor University], Hamed Soleymanabadi

Ammonia N–H bond cleavage at metal-free substrates has attracted great attention because of its industrial importance. Here, we investigate the dissociative adsorption of ammonia onto the surface of a B₃₆ borophene sheet by means of density functional theory calculations.

- 69 **Functional analysis of the binding model of microbial inulinases using docking and molecular dynamics simulation**, Puneet Kumar Singh, Josmi Joseph, Sukriti Goyal, Abhinav Grover, Pratyosh Shukla [Maharshi Dayanand University]

See Applications / Ligand Binding.

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Results

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About 100 Papers from more than 30 Journals are cited.

1 APPLICATIONS (69) Page 2

1.1 Small Molecules (17)

Genral and Model Systems	Page 2	QSAR	Page 5
Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 6

1.2 Biopolymers (52)

Bioinformatics and Cheminformatics	Page 7	Enzyme Catalysis	Page 12
Comparitive or Homology Modeling	Page 8	Protein-Protein Interactions	Page 16
Protein Conformational Analysis	Page 9	Membrane Proteins	Page 17
Protein Structure Analysis	Page 10	Protein Folding	Page 19
Protein Dynamics	Page 11	Protein-Nucleic Acids	Page 19
Ligand Binding	Page 12	Nucleic Acids	Page 20

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (17) Page 20

QSAR	Page 20	QM & QM/MM	Page 22
Potentials and Parameters	Page 21	Ligand Docking Modeling	Page 23
Free Energy Perturbation	Page 22		

3 JOURNAL REVIEWS (8) Page 44

Journal of Molecular Graphics and Modeling, 66, May, 2016.
 Journal of Computational Chemistry, 37 (13, 14), May, 2016.
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 Journal of Molecular Modeling, 22 (5), May, 2016.
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4 ADDRESSES OF PRINCIPAL AUTHORS Page 43

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

A Stochastic, Resonance-Free Multiple Time-Step Algorithm for Polarizable Models That Permits Very Large Time Steps

Daniel T. Margul and Mark E. Tuckerman [New York University]

J. Chem. Theor. and Comp., **12**, 2170–2180, 2016.

Molecular dynamics remains one of the most widely used computational tools in the theoretical molecular sciences to sample an equilibrium ensemble distribution and/or to study the dynamical properties of a system. In this paper, we develop a stochastic isokinetic algorithm for multiple time-step molecular dynamics calculations using a polarizable model based on fluctuating dipoles. The scheme developed here employs two sets of induced dipole moments, specifically, those associated with short-range interactions and those associated with a full set of interactions.

Medicinal Chemistry and Drug Design

3D-QSAR-aided design, synthesis, in vitro and in vivo evaluation of dipeptidyl boronic acid proteasome inhibitors and mechanism studies

Meng Lei, Huayun Feng, Cheng Wang, Hailing Li, Jingmiao Shi, Jia Wang, Zhaogang Liu, Shanshan Chen, Shihe Hu, Yongqiang Zhu [Nanjing Normal University]

Bioorg. and Med. Chem., **24**, 2576–2588, 2016

Proteasome had been clinically validated as an effective target for the treatment of cancers. Up to now, many structurally diverse proteasome inhibitors were discovered. And two of them were launched to treat multiple myeloma (MM) and mantle cell lymphoma (MCL). Based on our previous biological results of dipeptidyl boronic acid proteasome inhibitors, robust 3D-QSAR models were developed and structure–activity relationship (SAR) was summarized. Several structurally novel compounds were designed based on the theoretical models and finally synthesized.



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Medicinal Chemistry and Drug Design (Cont'd)

Discovery of a latent calcineurin inhibitory peptide from its autoinhibitory domain by docking, dynamic simulation, and in vitro methods

B. M. Harish, R. Saraswathi, D. Vinod & K. S. Devaraju
[Bangalore University, JB Campus]

J. Biomol. Stru. and Dyn., **34**, 983-992, 2016.

Autoinhibitory domain (AID) of calcineurin (CN) was discovered two decades ago. Fewer investigations are reported to find out shortest possible peptide from the AID for CN inhibition. Hence, this study has focused on screening of nearly 150 peptide fragments derived from the AID using in silico method. Therefore, we have employed docking studies, aiming to analyze the best pose of AID-derived peptides on CN active site. We also analyzed binding free energy (ΔG) of docked complex using molecular mechanics/generalized Born surface area (MM/GBSA). MM/GBSA predicts two short peptides P1 and P2 found to be lowest binding free energy.

Evaluation of potential flavonoid inhibitors of glyoxalase-I based on virtual screening and in vitro studies

Aarti Yadav, Rajnish Kumar, Aditya Sunkaria, Nitin Singhal, Manoj Kumar & Rajat Sandhir [Panjab University]

J. Biomol. Stru. and Dyn., **34**, 993-1007, 2016.

Glyoxalase-I (GLO-I) is a component of the ubiquitous detoxification system involved in the conversion of methylglyoxal (MG) to d-lactate in the glycolytic pathway. MG toxicity arises from its ability to form advanced glycation end products. GLO-I has been reported to be frequently overexpressed in various types of cancer cells. We performed structure-based virtual screening of focused flavonoids commercial library to identify potential and specific inhibitors of GLO-I.

Insight into the structural requirements of aminopyrimidine derivatives for good potency against both purified enzyme and whole cells of M. tuberculosis: combination of HQSAR, CoMSIA, and MD simulation studies

Auradee Punkvang [Nakhon Phanom University], Supa Hannongbua, Patchreenart Saparpakorn & Pornpan Pungpo

J. Biomol. Stru. and Dyn., **34**, 1079-1091, 2016.

The Mycobacterium tuberculosis protein kinase B (PknB) is critical for growth and survival of M. tuberculosis within the host. The series of aminopyrimidine derivatives show impressive activity against PknB ($IC_{50} < .5 \mu M$). However, most of them show weak or no cellular activity against M. tuberculosis ($MIC > 63 \mu M$). Consequently, the key structural features related to activity against of both PknB and M. tuberculosis need to be investigated. Here, two- and three-dimensional quantitative structure-activity relationship (2D and 3D QSAR) analyses combined with molecular dynamics (MD) simulations were employed with the aim to evaluate these key structural features of aminopyrimidine derivatives.

Discover natural compounds as potential phosphodiesterase-4B inhibitors via computational approaches

Jing Li, Nan Zhou, Wen Liu, Jianzong Li, Yu Feng, Xiaoyun Wang, Chuanfang Wu & Jinku Bao [Sichuan University]

J. Biomol. Stru. and Dyn., **34**, 1101-1112, 2016.

cAMP, intracellular cyclic adenosine monophosphate, is a ubiquitous second messenger that plays a key role in many physiological processes. PDE4B which can reduce the cAMP level by hydrolyzing cAMP to 5'-AMP has become a therapeutic target for the treatment of human diseases such as respiratory disorders, inflammation diseases, neurological and psychiatric disorders. However, the use of currently available PDE4B inhibitors is restricted due to serious side effects caused by targeting PDE4D. We are attempting to find out subfamily-selective PDE4B inhibitors from natural products, using computer-aided approaches such as virtual screening, docking, and MD simulations.

Medicinal Chemistry and Drug Design (Cont'd)

Influence of the R823W mutation on the interaction of the ANKS6-ANKS3: insights from molecular dynamics simulation and free energy analysis

Wei Kan [Qiqihar University], Fengqin Fang, Lin Chen, Ruige Wang & Qigang Deng

J. Biomol. Stru. and Dyn., **34**, 1113-1122, 2016.

The sterile alpha motif (SAM) domain of the protein ANKS6, a protein-protein interaction domain, is responsible for autosomal dominant polycystic kidney disease. Although the disease is the result of the R823W point mutation in the SAM domain of the protein ANKS6, the molecular details are still unclear. We applied molecular dynamics simulations, the principal component analysis, and the molecular mechanics Poisson-Boltzmann surface area binding free energy calculation to explore the structural and dynamic effects of the R823W point mutation on the complex ANKS6-ANKS3 (PDB ID: 4NL9) in comparison to the wild proteins.

Pharmacophore model prediction, 3D-QSAR and molecular docking studies on vinyl sulfones targeting Nrf2-mediated gene transcription intended for anti-Parkinson drug design

Mohd Athar, Mohsin Yousuf Lone, Vijay M. Khedkar & Prakash Chandra Jha [Central University of Gujarat]

J. Biomol. Stru. and Dyn., **34**, 1282-1297, 2016.

Despite intense research efforts towards clinical and molecular causes of Parkinson disease (PD), the etiology of disease still remains unclear. However, recent studies have provided ample evidences that the oxidative stress is the key player that contributes a lot to dopaminergic (DAergic) neurodegeneration in brain. It is due to the discrepancy of antioxidant defence system of which nuclear factor erythroid 2-related factor 2 (Nrf2) signalling is of central contour. In the current study, potent heme oxygenase-1 agonists (Nrf2 signalling regulator), vinyl sulfones, were selected and an optimal pharmacophore model was brought forth which was examined using a decoy set by atom-based 3D-QSAR.

Discovery of Novel 15-Lipoxygenase Activators To Shift the Human Arachidonic Acid Metabolic Network toward Inflammation Resolution

Hu Meng, Christopher L. McClendon, Ziwei Dai, Kenan Li, Xiaoling Zhang, Shan He, Erchang Shang, Ying Liu, and Luhua Lai [Peking University]

Jou. Med. Chem., **59**, 4202-4209, 2016.

For disease network intervention, up-regulating enzyme activities is equally as important as down-regulating activities. However, the design of enzyme activators presents a challenging route for drug discovery. Previous studies have suggested that activating 15-lipoxygenase (15-LOX) is a promising strategy to intervene the arachidonic acid (AA) metabolite network and control inflammation. To prove this concept, we used a computational approach to discover a previously unknown allosteric site on 15-LOX. Both allosteric inhibitors and novel activators were discovered using this site.

Fragment Molecular Orbital Method Applied to Lead Optimization of Novel Interleukin-2 Inducible T-Cell Kinase (ITK) Inhibitors

Alexander Heifetz, Giancarlo Trani, Matteo Aldeghe, Colin H. MacKinnon, Paul A. McEwan, Frederick A. Brookfield, Ewa I. Chudyk, Mike Bodkin, Zhonghua Pei, Jason D. Burch, and Daniel F. Ortwine [Discovery Chemistry, Genentech, Inc.]

Jou. Med. Chem., **59**, 4352-4363, 2016.

Inhibition of inducible T-cell kinase (ITK), a nonreceptor tyrosine kinase, may represent a novel treatment for allergic asthma. In our previous reports, we described the discovery of sulfonylpyridine (SAP), benzothiazole (BZT), indazole (IND), and tetrahydroindazole (THI) series as novel ITK inhibitors and how computational tools such as dihedral scans and docking were used to support this process. X-ray crystallography and modeling were applied to provide essential insight into ITK-ligand interactions.

Medicinal Chemistry and Drug Design (Cont'd)

Ole e 13 is the unique food allergen in olive: Structure-functional, substrates docking, and molecular allergenicity comparative analysis

J.C. Jimenez-Lopez [Spanish National Research Council], P. Robles-Bolivar, F.J. Lopez-Valverde, E. Lima-Cabello, S.O. Kotchoni, J.D. Alché

J. Mol.Graph. and Mod., **66**, 26-40, 2016.

Thaumatococcus-like proteins (TLPs) are enzymes with important functions in pathogens defense and in the response to biotic and abiotic stresses. Last identified olive allergen (Ole e 13) is a TLP, which may also importantly contribute to food allergy and cross-allergenicity to pollen allergen proteins. The goals of this study are the characterization of the structural-functionality of Ole e 13 with a focus in its catalytic mechanism, and its molecular allergenicity by extensive analysis using different molecular computer-aided approaches.

Virtual screening of eighteen million compounds against dengue virus: Combined molecular docking and molecular dynamics simulations study

Shaher Bano Mirza, Ramin Ekhteiari Salmas, M. Qaiser Fatmi, Serdar Durdagi [Bahcesehir University]

J. Mol.Graph. and Mod., **66**, 99-107, 2016.

Dengue virus is a major issue of tropical and sub-tropical regions. Dengue virus has been the cause behind the major alarming epidemics in the history with mass casualties from the decades. The protease enzyme pathway is the critical target for drug design due to its significance in the replication, survival and other cellular activities of dengue virus. Therefore, approximately eighteen million compounds from the ZINC database have been virtually screened against nonstructural protein 3 (NS3).

Interactions between pyrazole derived enantiomers and Chiralcel OJ: Prediction of enantiomer absolute configurations and elution order by molecular dynamics simulations

Guixiang Hu, Meilan Huang [Queen's University Belfast], Chengcai Luo, Qi Wang, Jian-Wei Zou

J. Mol.Graph. and Mod., **66**, 123-132, 2016.

The separation of enantiomers and confirmation of their absolute configurations is significant in the development of chiral drugs. The interactions between the enantiomers of chiral pyrazole derivative and polysaccharide-based chiral stationary phase cellulose tris(4-methylbenzoate) (Chiralcel OJ) in seven solvents and under different temperature were studied using molecular dynamics simulations. The results show that solvent effect has remarkable influence on the interactions.

Quantitative Structure-Activity Relations

Structural insights of a PI3K/mTOR dual inhibitor with the morpholino-triazine scaffold

Takako Takeda, Yanli Wang [National Institutes of Health], Stephen H. Bryant

J.Comp.Aided. Mol.des. **30**, 323-330, 2016.

Stimulation of the PI3K/Akt/mTOR pathway, which controls cell proliferation and growth, is often observed in cancer cell. Inhibiting both PI3K and mTOR in this pathway can switch off Akt activation and hence, plays a powerful role for modulating this pathway. PKI-587, a drug containing the structure of morpholino-triazines, shows a dual and nano-molar inhibition activity and is currently in clinical trial. To provide an insight into the mechanism of this dual inhibition, pharmacophore and QSAR models were developed in this work using compounds based on the morpholino-triazines scaffold, followed by a docking study.

QSAR (Cont'd)

A mechanism-based 3D-QSAR approach for classification and prediction of acetylcholinesterase inhibitory potency of organophosphate and carbamate analogs

Sehan Lee [U.S. Environmental Protection Agency], Mace G. Barron

J.Comp.Aided. Mol.des. **30**, 347-363, 2016.

Organophosphate (OP) and carbamate esters can inhibit acetylcholinesterase (AChE) by binding covalently to a serine residue in the enzyme active site, and their inhibitory potency depends largely on affinity for the enzyme and the reactivity of the ester. Despite this understanding, there has been no mechanism-based in silico approach for classification and prediction of the inhibitory potency of ether OPs or carbamates. This prompted us to develop a three dimensional prediction framework for OPs, carbamates, and their analogs. Inhibitory structures of a compound that can form the covalent bond were identified through analysis of docked conformations of the compound and its metabolites.

Carbon Nanoparticles

Curvature-dependent adsorption of water inside and outside armchair carbon nanotubes

Shulai Lei [Freie Universität Berlin], Beate Paulus, Shujuan Li and Burkhard Schmidt

J. Comp. Chem., **37**, 1313–1320, 2016.

The curvature dependence of the physisorption properties of a water molecule inside and outside an armchair carbon nanotube (CNT) is investigated by an incremental density-fitting local coupled cluster treatment with single and double excitations and perturbative triples (DF-LCCSD(T)) study. Our results show that a water molecule outside and inside (n, n) CNTs (n = 4, 5, 6, 7, 8, 10) is stabilized by electron correlation. The adsorption energy of water inside CNTs decreases quickly with the decrease of curvature (increase of radius) and the configuration with the oxygen pointing toward the CNT wall is the most stable one.

Charge-tunable insertion process of carbon nanotubes into DNA nanotubes

Lijun Liang, Zhisen Zhang, Zhe Kong, Yong Liu, Jia-Wei Shen, Debing Li, Qi Wang [Zhejiang University]

J. Mol.Graph. and Mod., **66**, 20-25, 2016.

Control over interactions with biomolecules holds the key of the applications of carbon nanotubes (CNTs) in biotechnology. Here we report a molecule dynamics study on the encapsulation process of different charged CNTs into DNA nanotubes. Our results demonstrated that insertion process of CNTs into DNA nanotubes are charge-tunable. The positive charged CNTs could spontaneously encapsulate and confined in the hollow of DNA nanotubes under the combination of electrostatic and vdW interaction in our ns scale simulation.

1.2. Biopolymers

Bioinformatics and Cheminformatics

MAESTROweb: a web server for structure-based protein stability prediction

Josef Laimer, Julia Hiebl-Flach, Daniel Lengauer, and Peter Lackner [University of Salzburg]

Bioinformatics. **32**, 1414-1416, 2016.

The prediction of change in stability upon point mutations in proteins has many applications in protein analysis and engineering. We now provide access to the most important features of MAESTRO by an easy to use web service. MAESTROweb allows the prediction of change in stability for user-defined mutations, provides a scan functionality for the most (de)stabilizing n-point mutations for a maximum of $n = 5$, creates mutation sensitivity profiles and evaluates potential disulfide bonds. MAESTROweb operates on monomers, multimers and biological assemblies as defined by PDB.

Electron tunneling in proteins program

Muhammad A. Hagra and Alexei A. Stuchebrukhov [University of California, Davis]

J. Comp. Chem., **37**, 1388–1395, 2016.

We developed a unique integrated software package (called Electron Tunneling in Proteins Program or ETP) which provides an environment with different capabilities such as tunneling current calculation, semi-empirical quantum mechanical calculation, and molecular modeling simulation for calculation and analysis of electron transfer reactions in proteins. ETP program is developed as a cross-platform client-server program in which all the different calculations are conducted at the server side while only the client terminal displays the resulting calculation outputs in the different supported representations.

Improvements in GROMACS plugin for PyMOL including implicit solvent simulations and displaying results of PCA analysis

Tomasz Makarewicz, Rajmund Kaźmierkiewicz [University of Gdańsk and Medical University of Gdańsk]

J. Mol.Mod., **22**, 109, 2016.

In order to get the dynamic molecule model from the static one, the molecular dynamics (MD) simulation needs to be performed. Some software sets such as GROMACS are used for that purpose. Unfortunately they lack GUI. The Dynamics PyMOL plugin allows researcher to perform MD simulations directly from the PyMOL software by GUI-based interface of GROMACS tools. This paper describes many improvements introduced into the Dynamics PyMOL plugin 2.0 including: an integration with ProDy library, possibility to use the implicit solvents, an ability to interpret the MD simulations, and implementation of some more GROMACS functionality.

Bioinformatics and Cheminformatics (Cont'd)

BROMOCEA Code: An Improved Grand Canonical Monte Carlo/Brownian Dynamics Algorithm Including Explicit Atoms

Carlos J. F. Solano, Karunakar R. Pothula, Jigneshkumar D. Prajapati, Pablo M. De Biase, Sergei Yu. Noskov, and Ulrich Kleinekathöfer [Jacobs University Bremen]

J. Chem. Theor. and Comp., **12**, 2401–2417, 2016.

All-atom molecular dynamics simulations have a long history of applications studying ion and substrate permeation across biological and artificial pores. While offering unprecedented insights into the underpinning transport processes, MD simulations are limited in time-scales and ability to simulate physiological membrane potentials or asymmetric salt solutions and require substantial computational power. In the present contribution, we report an extension of the Brownian dynamics scheme which includes conformational dynamics. To achieve this goal, the dynamics of amino-acid residues was incorporated into the many-body potential of mean force and into the Langevin equations of motion.

TaBoo SeArch Algorithm with a Modified Inverse Histogram for Reproducing Biologically Relevant Rare Events of Proteins

Ryuhei Harada, Yu Takano, and Yasuteru Shigeta [University of Tsukuba]

J. Chem. Theor. and Comp., **12**, 2436–2445, 2016.

The TaBoo SeArch (TBSA) algorithm [Harada et al. *J. Comput. Chem.* 2015, **36**, 763–772 and Harada et al. *Chem. Phys. Lett.* 2015, **630**, 68–75] was recently proposed as an enhanced conformational sampling method for reproducing biologically relevant rare events of a given protein. In this study, we propose a simple modification of the inverse histogram to further accelerate the convergence of TBSA.

Comparative or Homology Modeling

Homology modeling and molecular docking studies of *Drosophila* and *Aedes* sex peptide receptors

Jeong-hyun Kim, Soo-Kyung Kim, Jae-Hyuk Lee, Young-Joon Kim, William A. Goddard III, Yong-Chul Kim [Gwangju Institute of Science and Technology]

J. Mol. Graph. and Mod., **66**, 115–122, 2016.

The *Drosophila melanogaster* sex peptide receptor (DrmSPR), which is a G protein-coupled receptor (GPCR), is known as the specific receptor for sex peptide (SP). It is responsible for the reproductive behavior in the *Drosophila* model system; in particular, it is involved in the post-mating responses such as the increase in egg-laying ability and decrease in receptivity in females. To investigate the binding mechanism of the small molecule agonist of DrmSPR, the ensemble structures of low-lying packing structures of DrmSPR and *Aedes*SPR were assembled using the GEnSeMBLE (GPCR Ensemble of Structures in Membrane BiLayer Environment) method.

Physical nature of intermolecular interactions inside Sir2 homolog active site: molecular dynamics and *ab initio* study

Przemysław Czeleń, Żaneta Czyżnikowska [Wrocław Medical University]

J. Mol. Mod., **22**, 120, 2016.

In the present study, we analyze the interactions of NAD⁺-dependent deacetylase (Sir2 homolog yeast Hst2) with carba-nicotinamide-adenine-dinucleotide (ADP-HPD). For the Sir2 homolog, a yeast Hst2 docking procedure was applied. The structure of the protein–ADP-HPD complex obtained during the docking procedure was used as a starting point for molecular dynamics simulation. The intermolecular interaction energy partitioning was performed for protein–ADP-HPD complex resulting from molecular dynamics simulation.

Comparative or Homology Modeling (Cont'd)

Human Pyruvate Dehydrogenase Complex E2 and E3BP Core Subunits: New Models and Insights from Molecular Dynamics Simulations

Samira Hezaveh, An-Ping Zeng, and Uwe Jandt [Hamburg University of Technology]

J. Phys. Chem. B., **120**, 4399–4409, 2016.

Targeted manipulation and exploitation of beneficial properties of multienzyme complexes, especially for the design of novel and efficiently structured enzymatic reaction cascades, require a solid model understanding of mechanistic principles governing the structure and functionality of the complexes. This type of system-level and quantitative knowledge has been very scarce thus far. We utilize the human pyruvate dehydrogenase complex (hPDC) as a versatile template to conduct corresponding studies.

Protein Conformational Analysis

Investigation of the dynamics of the viral immediate-early protein 1 in different conformations and oligomerization states

Joachim D. Stump & Heinrich Sticht [Friedrich-Alexander-Universität]

J. Biomol. Stru. and Dyn., **34**, 1029-1041, 2016.

The viral immediate-early protein 1 (IE1) is crucial for efficient replication of cytomegalovirus (CMV). A recent crystal structure of the IE1 protein from rhesus CMV revealed that the protein exhibits a novel fold and crystallizes in two slightly different dimeric arrangements. Molecular dynamics simulations and energetic analyses performed in this study show that both dimers are stable and allowed us to identify a common set of five residues that appear particularly important for dimer formation.

A method for predicting protein conformational pathways by using molecular dynamics simulations guided by difference distance matrices

Yasushige Yonezawa [Kinki University]

J. Comp. Chem., **37**, 1139–1146, 2016.

Here, an efficient method that predicts natural transition pathways between two endpoint states of an allosteric protein has been proposed. This method helps create structures that bridge these endpoints through multiple iterative and unbiased molecular dynamics simulations with explicit water. Difference distance matrices provide an approach for identifying states involving concerted slow motion. A series of structures are readily generated along the transition pathways of adenylate kinase.

A genetic algorithm encoded with the structural information of amino acids and dipeptides for efficient conformational searches of oligopeptides

Xiao Ru, Ce Song and Zijong Lin [University of Science and Technology of China]

J. Comp. Chem., **37**, 1214–1222, 2016.

The genetic algorithm (GA) is an intelligent approach for finding minima in a highly dimensional parametric space. However, the success of GA searches for low energy conformations of biomolecules is rather limited so far. Herein an improved GA scheme is proposed for the conformational search of oligopeptides. A systematic analysis of the backbone dihedral angles of conformations of amino acids (AAs) and dipeptides is performed. The structural information is used to design a new encoding scheme to improve the efficiency of GA search.

Protein Conformational Analysis (Cont'd)

Protein side chain conformation predictions with an MMGBSA energy function

Thomas Gaillard, Nicolas Panel and Thomas Simonson
[Ecole Polytechnique, Palaiseau]

Proteins: Stru. Fun. & Bioinf., **84**, 803–819, 2016.

The prediction of protein side chain conformations from backbone coordinates is an important task in structural biology, with applications in structure prediction and protein design. It is a difficult problem due to its combinatorial nature. We study the performance of an “MMGBSA” energy function, implemented in our protein design program Proteus, which combines molecular mechanics terms, a Generalized Born and Surface Area (GBSA) solvent model, with approximations that make the model pairwise additive.

Pressure-induced conformational switch of an interfacial protein

Quentin R. Johnson, Richard J. Lindsay, Ricky B. Nellas and Tongye Shen [University of Tennessee]

Proteins: Stru. Fun. & Bioinf., **84**, 820–827, 2016.

A special class of proteins adopts an inactive conformation in aqueous solution and activates at an interface (such as the surface of lipid droplet) by switching their conformations. Lipase, an essential enzyme for breaking down lipids, serves as a model system for studying such interfacial proteins. The underlying conformational switch of lipase induced by solvent condition is achieved through changing the status of the gated substrate-access channel. Interestingly, a lipase was also reported to exhibit pressure activation, which indicates it is drastically active at high hydrostatic pressure.

Protein Structure Analysis

Prediction of Loops in G Protein-Coupled Receptor Homology Models: Effect of Imprecise Surroundings and Constraints

Bhumika Arora, Thomas Coudrat, Denise Wootten, Arthur Christopoulos, Santosh B. Noronha, and Patrick M. Sexton
[Monash University]

J.Chem. Infor. and Mod., **56**, 671–686, 2016.

In the present study, we explored the extent to which inaccuracies inherent in homology models of the transmembrane helical cores of G protein-coupled receptors (GPCRs) can impact loop prediction. We demonstrate that loop prediction in homology models is much more difficult than loop reconstruction in crystal structures because of the imprecise positioning of loop anchors. Deriving information from 17 recently available GPCR crystal structures, we estimated all of the possible errors that could occur in loop anchors as the result of comparative modeling.

Protein Dynamics

Timing Correlations in Proteins Predict Functional Modules and Dynamic Allostery

Milo M. Lin [University of Texas Southwestern Medical Center]

J. Am. Chem. Soc., **138**, 5036–5043, 2016.

How protein structure encodes functionality is not fully understood. For example, long-range intraprotein communication can occur without measurable conformational change and is often not captured by existing structural correlation functions. It is shown here that important functional information is encoded in the timing of protein motions, rather than motion itself. I introduce the conditional activity function to quantify such timing correlations among the degrees of freedom within proteins.

Investigation of flap flexibility of β -secretase using molecular dynamic simulations

Hezekiel M. Kumalo, Soumendranath Bhakat & Mahmoud E. Soliman [University of KwaZulu-Natal]

J. Biomol. Stru. and Dyn., **34**, 1008-1019, 2016.

Flap motif and its dynamics were extensively reported in aspartate proteases, e.g. HIV proteases and plasmepsins. Herein, we report the first account of flap dynamics amongst different conformations of β -secretase using molecular dynamics simulation. Three systems were studied, namely Free ($BACE_{Free}$) and two ligand-bound conformations, which belonged to space groups P6₁22 ($BACE_{Bound1}$) and C222₁ ($BACE_{Bound2}$), respectively and four parameters (distance between the flaps tip residue, Thr72 and Ser325, d_1 ; dihedral angle, ϕ) were proposed to understand the change in dynamics of flap domain and the extent of flap opening and closing.

Molecular insight into amyloid oligomer destabilizing mechanism of flavonoid derivative 2-(4' benzyloxyphenyl)-3-hydroxy-chromen-4-one through docking and molecular dynamics simulations

Akhil Kumar, Swati Srivastava, Shubhendra Tripathi, Sandeep Kumar Singh, Saripella Srikrishna & Ashok Sharma [CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP)]

J. Biomol. Stru. and Dyn., **34**, 1252-1263, 2016.

Aggregation of amyloid peptide ($A\beta$) has been shown to be directly related to progression of Alzheimer's disease (AD). $A\beta$ is neurotoxic and its deposition and aggregation ultimately lead to cell death. In our previous work, we reported flavonoid derivative (compound 1) showing promising result in transgenic AD model of *Drosophila*. Compound 1 showed prevention of $A\beta$ -induced neurotoxicity and neuroprotective efficacy in *Drosophila* system. However, mechanism of action of compound 1 and its effect on the amyloid is not known. We therefore performed molecular docking and atomistic, explicit-solvent molecular dynamics simulations to investigate the process of $A\beta$ interaction, inhibition, and destabilizing mechanism.

SOP-GPU: influence of solvent-induced hydrodynamic interactions on dynamic structural transitions in protein assemblies

Andrey Alekseenko, Olga Kononova, Yaroslav Kholodov, Kenneth A. Marx and Valeri Barsegov [University of Massachusetts]

J. Comp. Chem., **37**, 1537–1551, 2016.

Hydrodynamic interactions (HI) are incorporated into Langevin dynamics of the C_α -based protein model using the Truncated Expansion approximation (TEA) to the Rotne–Prager–Yamakawa diffusion tensor. Computational performance of the obtained GPU realization demonstrates the model's capability for describing protein systems of varying complexity (10^2 – 10^5 residues), including biological particles (filaments, virus shells). Comparison of numerical accuracy of the TEA versus exact description of HI reveals similar results for the kinetics and thermodynamics of protein unfolding.

Protein Dynamics (Cont'd)

pH dependence of ligand-induced human epidermal growth factor receptor activation investigated by molecular dynamics simulations

Jun Dong, Yonghui Zhang, Zhiyong Zhang [Hefei National Laboratory for Physical Science at Microscale and School of Life Sciences]

J. Mol.Mod., **22**, 131, 2016.

The activation of human epidermal growth factor receptor (hEGFR) involves a large conformational change in its soluble extracellular domains (sECD, residues 1–620), from a tethered to an extended conformation upon binding of ligands, such as EGF. It has been reported that this dynamic process is pH-dependent, that is, hEGFR can be activated by EGF at high pH to form an extended dimer but remains as an inactive monomer at low pH. In this paper, we perform all-atom MD simulations starting from the tethered conformation of sECD:EGF complex, at pH 5.0 and 8.5, respectively.

Coarse-grained modeling of the intrinsically disordered protein Histatin 5 in solution: Monte Carlo simulations in combination with SAXS

Carolina Cragnell [Lund University], Dominique Durand, Bernard Cabane and Marie

Proteins: Stru. Fun. & Bioinf., **84**, 777–791, 2016.

Monte Carlo simulations and coarse-grained modeling have been used to analyze Histatin 5, an unstructured short cationic salivary peptide known to have anticandidal properties. The calculated scattering functions have been compared with intensity curves and the distance distribution function $P(r)$ obtained from small angle X-ray scattering (SAXS), at both high and low salt concentrations. The aim was to achieve a molecular understanding and a physico-chemical insight of the obtained SAXS results and to gain information of the conformational changes of Histatin 5 due to altering salt content, charge distribution, and net charge.

Ligand Binding/Docking

Molecular modelling of human 5-hydroxytryptamine receptor (5-HT_{2A}) and virtual screening studies towards the identification of agonist and antagonist molecules

A. Gandhimathi & R. Sowdhamini [National Centre for Biological Sciences (TIFR), GKVK Campus]

J. Biomol. Stru. and Dyn., **34**, 952-970, 2016.

The serotonin receptors, also known as 5-hydroxytryptamine (5-HT) receptors, are a group of G protein-coupled receptors (GPCRs) and ligand-gated ion channels found in the central and peripheral nervous systems. GPCRs have a characteristic feature of activating different signalling pathways upon ligand binding and these ligands display several efficacy levels to differentially activate the receptor. Here, we have performed the ligand interaction study using the two prominent states of GPCR, namely the active and inactive state of the 5-HT_{2A} receptor.

Noninvasive cellular internalization of silver molecules by chitosan nanoneedles: a novel nanocarrier

B.S. Wakure [Bharati Vidyapeeth's College of Pharmacy], N.M. Bhatia & Hussain Basha Syed

J. Biomol. Stru. and Dyn., **34**, 971-982, 2016.

We explore with molecular modeling, dynamics simulations, and a statistical model the ability of chitosan nanoneedles (CNNs) to be internalized into a model lipid bilayer as a function of their length, keeping in view of their applications for advanced targeted drug delivery. In this study, we have computationally modeled and studied the structural geometry and the stability of CNNs formed by 4, 6, and 8 subunits. Our MD simulation studies marched the ability of CNNs to translocate silver nanoparticles through biological membrane in a similar manner that resembles cell-penetrating peptides.

Ligand Binding / Docking (Cont'd)

Molecular dynamics investigations of BioH protein substrate specificity for biotin synthesis

Qiao Xue, Ying-Lu Cui, Qing-Chuan Zheng [Jilin University] & Hong-Xing Zhang

J. Biomol. Stru. and Dyn., **34**, 1052-1060, 2016.

BioH, an enzyme of biotin synthesis, plays an important role in fatty acid synthesis which assembles the pimelate moiety. Pimeloyl-acyl carrier protein (ACP) methyl ester, which is long known to be a biotin precursor, is the physiological substrate of BioH. Azeloyl methyl ester, which has a longer chain than pimeloyl methyl ester, conjugated to ACP is also indeed accepted by BioH with very low rate of hydrolysis. We have investigated chain elongation effects on the structures by using the fully atomistic molecular dynamics simulations combined with binding free energy calculations.

Structural investigations into the binding mode of novel neolignans Cmp10 and Cmp19 microtubule stabilizers by in silico molecular docking, molecular dynamics, and binding free energy calculations

Shubhendra Tripathi, Akhil Kumar, B. Sathish Kumar, Arvind S. Negi & Ashok Sharma [CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP)]

J. Biomol. Stru. and Dyn., **34**, 1232-1240, 2016.

Microtubule stabilizers provide an important mode of treatment via mitotic cell arrest of cancer cells. Recently, we reported two novel neolignans derivatives Cmp10 and Cmp19 showing anticancer activity and working as microtubule stabilizers at micromolar concentrations. In this study, we have explored the binding site, mode of binding, and stabilization by two novel microtubule stabilizers Cmp10 and Cmp19 using in silico molecular docking, molecular dynamics (MD) simulation, and binding free energy calculations.

Adaptive BP-Dock: An Induced Fit Docking Approach for Full Receptor Flexibility

Ashini Bolia and S. Banu Ozkan [Arizona State University, Tempe]

J.Chem. Infor. and Mod., **56**, 734–746, 2016.

We present an induced fit docking approach called Adaptive BP-Dock that integrates perturbation response scanning (PRS) with the flexible docking protocol of RosettaLigand in an adaptive manner. We first perturb the binding pocket residues of a receptor and obtain a new conformation based on the residue response fluctuation profile using PRS. Next, we dock a ligand to this new conformation by RosettaLigand, where we repeat these steps for several iterations.

Binding Mode and Induced Fit Predictions for Prospective Computational Drug Design

Christoph Grebner, Jessica Iegre, Johan Ulander, Karl Edman, Anders Hogner, and Christian Tyrchan [AstraZeneca R&D]

J.Chem. Infor. and Mod., **56**, 774–787, 2016.

Computer-aided drug design plays an important role in medicinal chemistry to obtain insights into molecular mechanisms and to prioritize design strategies. Although significant improvement has been made in structure based design, it still remains a key challenge to accurately model and predict induced fit mechanisms. The current study presents a systematic and exhaustive investigation of predicting binding modes for a range of systems using PELE (Protein Energy Landscape Exploration), an efficient and fast protein–ligand sampling algorithm.

Ligand Binding / Docking (Cont'd)

Computational analysis of EBNA1 “druggability” suggests novel insights for Epstein-Barr virus inhibitor design

Eleonora Gianti [University of the Sciences, Philadelphia],
Troy E. Messick, Paul M. Lieberman, Randy J. Zauhar

J.Comp.Aided. Mol.des. **30**, 285-303, 2016.

The Epstein-Barr Nuclear Antigen 1 (EBNA1) is a critical protein encoded by the Epstein-Barr Virus (EBV). During latent infection, EBNA1 is essential for DNA replication and transcription initiation of viral and cellular genes and is necessary to immortalize primary B-lymphocytes. We conducted computational identification and structural characterization of EBNA1 binding pockets, likely to accommodate ligand molecules (i.e. “druggable” binding sites).

Enzyme Catalysis

Structural and mechanistic analysis of engineered trichodiene synthase enzymes from *Trichoderma harzianum*: towards higher catalytic activities empowering sustainable agriculture

Indu Kumari, Nitika Chaudhary, Padmani Sandhu, Mushtaq Ahmed & Yusuf Akhter [Central University of Himachal Pradesh]

J. Biomol. Stru. and Dyn., **34**, 1176-1189, 2016.

Trichoderma spp. are well-known bioagents for the plant growth promotion and pathogen suppression. The beneficial activities of the fungus *Trichoderma* spp. are attributed to their ability to produce and secrete certain secondary metabolites such as trichodermin that belongs to trichothecene family of molecules. In this study, we have carried out a comprehensive comparative sequence and structural analysis of the TS, which revealed the conserved residues involved in catalytic activity of the protein.

Combined QM(DFT)/MM molecular dynamics simulations of the deamination of cytosine by yeast cytosine deaminase (yCD)

Xin Zhang, Yuan Zhao, Honggao Yan, Zexing Cao and Yirong Mo [Western Michigan University]

J. Comp. Chem., **37**, 1163–1174, 2016.

Extensive combined quantum mechanical (B3LYP/6-31G*) and molecular mechanical (QM/MM) molecular dynamics simulations have been performed to elucidate the hydrolytic deamination mechanism of cytosine to uracil catalyzed by the yeast cytosine deaminase (yCD). Though cytosine has no direct binding to the zinc center, it reacts with the water molecule coordinated to zinc, and the adjacent conserved Glu64 serves as a general acid/base to shuttle protons from water to cytosine. The overall reaction consists of several proton-transfer processes and nucleophilic attacks.

Determination of the protonation state for the catalytic dyad in β -secretase when bound to hydroxyethylamine transition state analogue inhibitors: A molecular dynamics simulation study

Carlos Gueto-Tettay [Universidad de Cartagena], Roberto Pestana-Nobles, Juan Carlos Drosos-Ramirez

J. Mol.Graph. and Mod., **66**, 155-167, 2016.

BACE1 is an aspartyl protease of pharmacological interest for its direct participation in Alzheimer's disease (AD) through β -amyloid peptide production. Two aspartic acid residues are present in the BACE1 catalytic region which can adopt multiple protonation states depending on the chemical nature of its inhibitors, i.e., monoprotonated, diprotonated and di-deprotonated states. In the present study a series of protein-ligand molecular dynamics (MD) simulations was carried out to identify the most feasible protonation state adopted by the catalytic dyad in the presence of hydroxyethylamine transition state analogue inhibitors.

Enzyme Catalysis (Cont'd)

QM/MM investigation of the catalytic mechanism of angiotensin-converting enzyme

Xia Mu, Chunchun Zhang, Dingguo Xu [Sichuan University]

J. Mol.Mod., **22**, 132, 2016.

Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II and degrades bradykinin and other vasoactive peptides. ACE inhibitors are used to treat diseases such as hypertension and heart failure. It is thus highly desirable to understand the catalytic mechanism of ACE, as this should facilitate the design of more powerful and selective ACE inhibitors. ACE exhibits two different active domains, the C-domain and the N-domain. In this work, we systematically investigated the inhibitor- and substrate-binding patterns in the N-domain of human ACE using a combined quantum mechanical and molecular mechanical approach.

Lytic Polysaccharide Monooxygenases ScLPMO10B and ScLPMO10C Are Stable in Ionic Liquids As Determined by Molecular Simulations

K.G. Sprenger, Alaksh Choudhury, Joel L. Kaar, and Jim Pfaendtner [University of Washington, Seattle]

J. Phys. Chem. B., **120**, 3863–3872, 2016.

Lytic polysaccharide monooxygenases (LPMOs) are a newly discovered family of enzymes proposed to work synergistically with cellulases and aid in the decomposition of cellulose for the creation of environmentally friendly fuels and chemicals. To our knowledge, evaluation of the stability of LPMOs in ionic liquid (IL) solvents at relevant biomass processing conditions has not been explored. Herein, molecular dynamics simulations of ScLPMO10B and ScLPMO10C in three ILs at 10 and 20 wt% in water and in pure water have been performed. Enzyme stability was predicted to be high on the basis of structural and dynamic analyses we performed.

Aminoacetylation Reaction Catalyzed by Leucyl-tRNA Synthetase Operates via a Self-Assisted Mechanism Using a Conserved Residue and the Aminoacyl Substrate

Alexey Aleksandrov [UMR 7654, Ecole Polytechnique], Andrés Palencia, Stephen Cusack, and Martin Field

J. Phys. Chem. B., **120**, 4388–4398, 2016.

Leucyl-tRNA synthetase catalyzes attachment of leucine amino acid to its cognate tRNA. During the second, aminoacetylation, step of the reaction, the leucyl moiety is transferred from leucyl-adenylate to the terminal A76 adenosine of tRNA. In this work, we have investigated the aminoacetylation step catalyzed by leucyl-tRNA synthase, using ab initio quantum chemical/molecular mechanical hybrid potentials in conjunction with reaction-path-location algorithms and molecular dynamics free energy simulations.

Crystal structure of the deglycating enzyme Amadoriase I in its free form and substrate-bound complex

Federica Rigoldi, Alfonso Gautieri, Andrea Dalle Vedove, Anna Paola Lucarelli, Simone Vesentini and Emilio Parisini [Istituto Italiano Di Tecnologia, Milano]

Proteins: Stru. Fun. & Bioinf., **84**, 744–758, 2016.

Amadoriases, also known as fructosyl amine oxidases (FAOX), are enzymes that catalyze the de-glycosylation of fructosyl amino acids. However, mostly because of the lack of a complete structural characterization of the different members of the family, the molecular bases of their substrate specificity have yet to be fully understood. The high resolution crystal structures of the free and the substrate-bound form of Amadoriase I shown herein allow for the identification of key structural features that account for the diverse substrate specificity shown by this class of enzymes.

Enzyme Catalysis (Cont'd)

Identification of the active site of human mitochondrial malonyl-coenzyme a decarboxylase: A combined computational study

Baoping Ling, Yuxia Liu, Xiaoping Li, Zhiguo Wang and Siwei Bi [Qufu Normal University]

Proteins: Stru. Fun. & Bioinf., **84**, 792–802, 2016.

Malonyl-CoA decarboxylase (MCD) can control the level of malonyl-CoA in cell through the decarboxylation of malonyl-CoA to acetyl-CoA, and plays an essential role in regulating fatty acid metabolism, thus it is a potential target for drug discovery. However, the interactions of MCD with CoA derivatives are not well understood owing to unavailable crystal structure with a complete occupancy in the active site. To identify the active site of MCD, molecular docking and molecular dynamics simulations were performed to explore the interactions of human mitochondrial MCD (HmMCD) and CoA derivatives.

Protein-Protein Interactions

Path2PPI: an R package to predict protein–protein interaction networks for a set of proteins

Oliver Philipp, Heinz D. Osiewacz, and Ina Koch [Goethe-University]

Bioinformatics. **32**, 1427–1429, 2016.

We introduce Path2PPI, a new R package to identify protein–protein interaction (PPI) networks for fully sequenced organisms for which nearly none PPI are known. Path2PPI predicts PPI networks based on sets of proteins from well-established model organisms, providing an intuitive visualization and usability. It can be used to combine and transfer information of a certain pathway or biological process from several reference organisms to one target organism.

Sequence-based prediction of protein–peptide binding sites using support vector machine

Ghazaleh Taherzadeh, Yuedong Yang, Tuo Zhang, Alan Wee-Chung Liew and Yaoqi Zhou [Griffith University, Southport]

J. Comp. Chem., **37**, 1223–1229, 2016.

Protein–peptide interactions are essential for all cellular processes including DNA repair, replication, gene-expression, and metabolism. As most protein–peptide interactions are uncharacterized, it is cost effective to investigate them computationally as the first step. All existing approaches for predicting protein–peptide binding sites, however, are based on protein structures despite the fact that the structures for most proteins are not yet solved. This article proposes the first machine-learning method called SPRINT to make Sequence-based prediction of Protein–peptide Residue-level Interactions.

Investigating the importance of Delaunay-based definition of atomic interactions in scoring of protein–protein docking results

Rahim Jafari [Tarbiat Modares University], Mehdi Sadeghi, Mehdi Mirzaie

J. Mol.Graph. and Mod., **66**, 108–114, 2016.

The approaches taken to represent and describe structural features of the macromolecules are of major importance when developing computational methods for studying and predicting their structures and interactions. This study attempts to explore the significance of Delaunay tessellation for the definition of atomic interactions by evaluating its impact on the performance of scoring protein–protein docking prediction. Two sets of knowledge-based scoring potentials are extracted from a training dataset of native protein–protein complexes.

Membrane Proteins and Lipid Peptide Interactions

Interaction Entropy: A New Paradigm for Highly Efficient and Reliable Computation of Protein–Ligand Binding Free Energy

Lili Duan, Xiao Liu, and John Z.H. Zhang [East China Normal University]

J. Am. Chem. Soc., **138**, 5722–5728, 2016.

Efficient and reliable calculation of protein–ligand binding free energy is a grand challenge in computational biology and is of critical importance in drug design and many other molecular recognition problems. The main challenge lies in the calculation of entropic contribution to protein–ligand binding or interaction systems. In this report, we present a new interaction entropy method which is theoretically rigorous, computationally efficient, and numerically reliable for calculating entropic contribution to free energy in protein–ligand binding and other interaction processes.

Structure-Based Design of Peptidic Inhibitors of the Interaction between CC Chemokine Ligand 5 (CCL5) and Human Neutrophil Peptides 1 (HNP1)

Kanin Wichapong [Maastricht University], Jean-Eric Alard, Almudena Ortega-Gomez, Christian Weber, Tilman M. Hackeng, Oliver Soehnlein, and Gerry A. F. Nicolaes

Jou. Med. Chem., **59**, 4289–4301, 2016.

Protein–protein interactions (PPIs) are receiving increasing interest, much sparked by the realization that they represent druggable targets. Recently, we successfully developed a peptidic inhibitor, RRYGTSKYQ (“SKY” peptide), that shows high potential in vitro and in vivo to interrupt a PPI between the platelet-borne chemokine CCL5 and the neutrophil-derived granule protein HNP1. This PPI plays a vital role in monocyte adhesion, representing a key mechanism in acute and chronic inflammatory diseases. Here, we present extensive and detailed computational methods applied to develop the SKY peptide.

Simulation-Based Approaches for Determining Membrane Permeability of Small Compounds

Christopher T. Lee, Jeffrey Comer, Conner Herndon, Nelson Leung, Anna Pavlova, Robert V. Swift, Chris Tung, Christopher N. Rowley, Rommie E. Amaro, Christophe Chipot, Yi Wang, and James C. Gumbart [Georgia Institute of Technology]

J.Chem. Infor. and Mod., **56**, 721–733, 2016.

Predicting the rate of nonfacilitated permeation of solutes across lipid bilayers is important to drug design, toxicology, and signaling. These rates can be estimated using molecular dynamics simulations combined with the inhomogeneous solubility-diffusion model, which requires calculation of the potential of mean force and position-dependent diffusivity of the solute along the transmembrane axis. In this paper, we assess the efficiency and accuracy of several methods for the calculation of the permeability of a model DMPC bilayer to urea, benzoic acid, and codeine.

Improved Side Chain Dynamics in MARTINI Simulations of Protein–Lipid Interfaces

Florian A. Herzog, Lukas Braun, Ingmar Schoen, and Viola Vogel [Department of Health Sciences and Technology, ETH Zurich]

J. Chem. Theor. and Comp., **12**, 2446–2458, 2016.

Specific interactions of protein side chains and lipid membranes regulate the localization, orientation, and activity of many peripheral proteins. Here, we introduce a modification of the coarse-grained MARTINI protein model, called ‘side chain fix’ (scFix), that was necessary and sufficient to correctly sample the side chain dynamics of β -strands in several globular proteins. When compared to μ s long atomistic simulations or previous experimental findings, scFix MARTINI simulations reproduced all key interactions between the well-studied PLC- δ 1 pleckstrin homology domain and a phosphatidylinositol-4,5-bisphosphate (PIP2) containing lipid membrane.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Binding Energy Distribution Analysis Method: Hamiltonian Replica Exchange with Torsional Flattening for Binding Mode Prediction and Binding Free Energy Estimation

Ahmet Mentes, Nan-Jie Deng, R. S. K. Vijayan, Junchao Xia, Emilio Gallicchio, and Ronald M. Levy [Temple University, Philadelphia]

J. Chem. Theor. and Comp., **12**, 2459–2470, 2016.

Molecular dynamics modeling of complex biological systems is limited by finite simulation time. The simulations are often trapped close to local energy minima separated by high energy barriers. Here, we introduce Hamiltonian replica exchange (H-REMD) with torsional flattening in the Binding Energy Distribution Analysis Method (BEDAM), to reduce energy barriers along torsional degrees of freedom and accelerate sampling of intramolecular degrees of freedom relevant to protein–ligand binding. The method is tested on a standard benchmark (T4 Lysozyme/L99A/p-xylene complex) and on a library of HIV-1 integrase complexes derived from the SAMPL4 blind challenge.

MARTINI Coarse-Grained Model of Triton TX-100 in Pure DPPC Monolayer and Bilayer Interfaces

Antonio Pizzirusso, Antonio De Nicola [Università di Salerno], and Giuseppe Milano

J. Phys. Chem. B., **120**, 3821–3832, 2016.

The coarse-grained MARTINI model of Triton TX-100 has been validated by direct comparison of the experimental and calculated area increase in pure DPPC lipid bilayers and monolayers at water/air interfaces in the presence of surfactant and by comparison of electron density profiles calculated with more detailed atomistic models based on the CHARMM force field. Bilayer simulations have been performed and compared with monolayers and with atomistic models.

A Critical Comparison of Biomembrane Force Fields: Structure and Dynamics of Model DMPC, POPC, and POPE Bilayers

Kristyna Pluhackova, Sonja A. Kirsch, Jing Han, Liping Sun, Zhenyan Jiang, Tobias Unruh, and Rainer A. Böckmann [Friedrich-Alexander-University of Erlangen-Nürnberg]

J. Phys. Chem. B., **120**, 3888–3903, 2016.

Atomistic molecular dynamics simulations have become an important source of information for the structure and dynamics of biomembranes at molecular detail difficult to access in experiments. A number of force fields for lipid membrane simulations have been derived in the past; the choice of the most suitable force field is, however, frequently hampered by the availability of parameters for specific lipids. Here, we compare four atomistic lipid force fields, namely, the united-atom GROMOS54a7 and the all-atom force fields CHARMM36, Slipids, and Lipid14, for a broad range of structural and dynamical properties of saturated and monounsaturated phosphatidylcholine bilayers (DMPC and POPC) as well as for monounsaturated phosphatidylethanolamine bilayers (POPE).

Effects of Transmembrane α -Helix Length and Concentration on Phase Behavior in Four-Component Lipid Mixtures: A Molecular Dynamics Study

David G. Ackerman and Gerald W. Feigenson [Cornell University, Ithaca]

J. Phys. Chem. B., **120**, 4064–4077, 2016.

We used coarse-grained molecular dynamics simulations to examine the effects of transmembrane α -helical WALP peptides on the behavior of four-component lipid mixtures. These mixtures contain a high-melting temperature (high- T_m) lipid, a nanodomain-inducing low- T_m lipid, a macrodomain-inducing low- T_m lipid and cholesterol to model the outer leaflet of cell plasma membranes. In a series of simulations, we incrementally replace the nanodomain-inducing low- T_m lipid by the macrodomain-inducing low- T_m lipid and measure how lipid and phase properties are altered by the addition of WALPs of different length.

Protein Folding

Markov State Models and tICA Reveal a Nonnative Folding Nucleus in Simulations of NuG2

Christian R. Schwantes, Diwakar Shukla, Vijay S. Pande [Stanford University]

Biophysical Journal., **110**, 1716-1719, 2016.

After reanalyzing simulations of NuG2—a designed mutant of protein G—generated by Lindorff-Larsen et al. with time structure-based independent components analysis and Markov state models as well as performing 1.5 ms of additional sampling on Folding@home, we found an intermediate with a register-shift in one of the β -sheets that was visited along a minor folding pathway. The minor folding pathway was initiated by the register-shifted sheet, which is composed of solely nonnative contacts, suggesting that for some peptides, nonnative contacts can lead to productive folding events.

Identification of putative unfolding intermediates of the mutant His-107-tyr of human carbonic anhydrase II in a multidimensional property space

Puspita Halder and Srabani Taraphder [Indian Institute of Technology, Kharagpur]

Proteins: Stru. Fun. & Bioinf., **84**, 726–743, 2016.

In this article, we develop an extensive search procedure of the multi-dimensional folding energy landscape of a protein. Our aim is to identify different classes of structures that have different aggregation propensities and catalytic activity. Following earlier studies by Daggett et al. [Jong, D. D.; Riley, R.; Alonso, D.O.; Daggett, V. J. *Mol. Biol.* 2002, 319, 229], a series of high temperature all-atom classical molecular simulation studies has been carried out to derive a multi-dimensional property space. Dynamical changes in these properties are then monitored by projecting them along a one-dimensional reaction coordinate, d_{mean} .

Protein-Nucleic acid Interactions

Zinc finger protein binding to DNA: an energy perspective using molecular dynamics simulation and free energy calculations on mutants of both zinc finger domains and their specific DNA bases

Mazen Y. Hamed [Birzeit University] & Gaurav Arya

J. Biomol. Stru. and Dyn., **34**, 919-934, 2016.

Energy calculations based on MM-GBSA were employed to study various zinc finger protein (ZF) motifs binding to DNA. Mutants of both the DNA bound to their specific amino acids were studied. Calculated energies gave evidence for a relationship between binding energy and affinity of ZF motifs to their sites on DNA. The mutations in the DNA bases reduced the value of the negative energies of binding (maximum value for $\Delta\Delta G = 42\text{Kcal/mol}$ for F1 when GCG mutated to GGG, and $\Delta\Delta G = 22\text{ kcal/mol}$ for F2, the loss in total energy of binding originated in the loss in electrostatic energies upon mutation ($r = .98$).

Flexibility–rigidity index for protein–nucleic acid flexibility and fluctuation analysis

Kristopher Opron, Kelin Xia, Zach Burton and Guo-Wei Wei [The Ohio State University]

J. Comp. Chem., **37**, 1283–1295, 2016.

Protein–nucleic acid complexes are important for many cellular processes including the most essential functions such as transcription and translation. For many protein–nucleic acid complexes, flexibility of both macromolecules has been shown to be critical for specificity and/or function. The flexibility-rigidity index (FRI) has been proposed as an accurate and efficient approach for protein flexibility analysis. In this article, we introduce FRI for the flexibility analysis of protein–nucleic acid complexes.

Nucleic Acids

Inosine Nucleobase Acts as Guanine in Interactions with Protein Side Chains

Matea Hajnic, Anita de Ruiter, Anton A. Polyansky, and Bojan Zagrovic [University of Vienna]

J. Am. Chem. Soc., **138**, 5519–5522, 2016.

A central intermediate in purine catabolism, the inosine nucleobase hypoxanthine is also one of the most abundant modified nucleobases in RNA and plays key roles in the regulation of gene expression and determination of cell fate. It is known that hypoxanthine acts as guanine when interacting with other nucleobases and base pairs most favorably with cytosine. Here we present for the first time the absolute binding free energies and the associated interaction modes between hypoxanthine and all standard, non-glycyl/non-prolyl amino acid side chain analogs as derived from molecular dynamics simulations and umbrella sampling in high- and low-dielectric environments.

Effect of temperature on the structure and hydration layer of TATA-box DNA: A molecular dynamics simulation study

Sudipta Samanta [Massachusetts Institute of Technology, Cambridge], Devanathan Raghunathan, Sanchita Mukherjee

J. Mol. Graph. and Mod., **66**, 9-19, 2016.

DNA within the living cells experiences a diverse range of temperature, ranging from freezing condition to hot spring water. How the structure, the mechanical properties of DNA, and the solvation dynamics around DNA changes with the temperature is important to understand the functionality of DNA under those acute temperature conditions. In that notion, we have carried out molecular dynamics simulations of a DNA oligomer, containing TATA-box sequence for three different temperatures (250 K, 300 K and 350 K).

2. METHODOLOGY

Quantitative Structure-Activity Relations

Development and validation of hydrophobic molecular fields derived from the quantum mechanical IEF/PCM-MST solvation models in 3D-QSAR

Tiziana Ginex, Jordi Muñoz-Muriedas, Enric Herrero, Enric Gibert, Pietro Cozzini and F. J. Luque [University of Barcelona]

J. Comp. Chem., **37**, 1147–1162, 2016.

Since the development of structure–activity relationships about 50 years ago, 3D-QSAR methods belong to the most refined ligand-based in silico techniques for prediction of biological data using physicochemical molecular fields. In this scenario, this study reports the development and validation of quantum mechanical (QM)-based hydrophobic descriptors derived from the parametrized MST continuum solvation model to be used in 3D-QSAR studies within the framework of the Hydrophobic Pharmacophore (HyPhar) method. To this end, five sets of compounds reported in the literature (dopamine D2/D4 antagonists, antifungal 2-aryl-4-chromanones, and inhibitors of GSK-3, cruzain and thermolysin) have been revisited.

Quantitative Structure-Activity Relations (Cont'd)

Using DFT methodology for more reliable predictive models: Design of inhibitors of Golgi α -Mannosidase II

Adela Bobovská, Igor Tvaroška, Juraj Kóna [Slovak Academy of Sciences]

J. Mol.Graph. and Mod., **66**, 47-57, 2016.

Human Golgi α -mannosidase II (GMII), a zinc ion co-factor dependent glycoside hydrolase (E.C.3.2.1.114), is a pharmaceutical target for the design of inhibitors with anti-cancer activity. The discovery of an effective inhibitor is complicated by the fact that all known potent inhibitors of GMII are involved in unwanted co-inhibition with lysosomal α -mannosidase (LMan, E.C.3.2.1.24), a relative to GMII. Therefore, we have developed a fast computational protocol to build predictive models combining interaction energy descriptors from an empirical docking scoring function (Glide-Schrödinger), Linear Interaction Energy (LIE) method, and quantum mechanical density functional theory (QM-DFT) calculations.

Docking, QM/MM, and molecular dynamics simulations of the hexose transporter from *Plasmodium falciparum* (PfHT)

Amanda Luisa da Fonseca [Universidade Federal de São João del-Rei], Renata Rachide Nunes, Vanildo Martins Lima Braga, Moacyr Comar Jr, Ricardo José Alves, Fernando de Pilla Varotti, Alex Gutterres Taranto

J. Mol.Graph. and Mod., **66**, 174-186, 2016.

Malaria is the most prevalent parasitic disease in the world. Currently, an effective vaccine for malaria does not exist, and chemotherapy must be used to treat the disease. This study aims to determine the three-dimensional structure of PfHT and to describe the intermolecular interactions between active glycoside derivatives and PfHT. Such information should aid in the development of new antimalarial drugs.

Alignment-independent technique for 3D QSAR analysis

Jon G. Wilkes [National Center for Toxicological Research], Iva B. Stoyanova-Slavova, Dan A. Buzatu

J.Comp.Aided. Mol.des. **30**, 331-345, 2016.

Molecular biochemistry is controlled by 3D phenomena but structure-activity models based on 3D descriptors are infrequently used for large data sets because of the computational overhead for determining molecular conformations. A diverse dataset of 146 androgen receptor binders was used to investigate how different methods for defining molecular conformations affect the performance of 3D-quantitative spectral data activity relationship models.

Potentials and Parameters

Reparameterizations of the χ Torsion and Lennard-Jones σ Parameters Improve the Conformational Characteristics of Modified Uridines

Indrajit Deb, Rupak Pal, Joanna Sarzynska and Ansuman Lahiri [University of Calcutta, Kolkata]

J. Comp. Chem., **37**, 1576–1588, 2016.

The currently available force field parameters for modified RNA residues in AMBER show significant deviations in conformational properties from experimental observations. The examination of the transferability of the recently revised torsion parameters revealed that there was an overall improvement in the conformational properties for some of the modifications but the improvements were still insufficient in describing the sugar pucker preferences (*J. Chem. Inf. Model.* **2014**, *54*, 1129–1142). Here, we report an approach for the development and fine tuning of the AMBER force field parameters for 2-thiouridine, 4-thiouridine, and pseudouridine with diverse conformational preferences.

Potentials and Parameters (Cont'd)

Role of Molecular Dynamics and Related Methods in Drug Discovery

Marco De Vivo [Istituto Italiano di Tecnologia], Matteo Masetti, Giovanni Bottegoni, and Andrea Cavalli

Jou. Med. Chem., **59**, 4035–4061, 2016.

Molecular dynamics (MD) and related methods are close to becoming routine computational tools for drug discovery. Their main advantage is in explicitly treating structural flexibility and entropic effects. This allows a more accurate estimate of the thermodynamics and kinetics associated with drug–target recognition and binding, as better algorithms and hardware architectures increase their use. Here, we review the theoretical background of MD and enhanced sampling methods, focusing on free-energy perturbation, metadynamics, steered MD, and other methods most consistently used to study drug–target binding.

Free Energy Perturbation

Converging ligand-binding free energies obtained with free-energy perturbations at the quantum mechanical level

Martin A. Olsson, Pär Söderhjelm and Ulf Ryde [Lund University]

J. Comp. Chem., **37**, 1589–1600, 2016.

In this article, the convergence of quantum mechanical (QM) free-energy simulations based on molecular dynamics simulations at the molecular mechanics (MM) level has been investigated. We have estimated relative free energies for the binding of nine cyclic carboxylate ligands to the octa-acid deep-cavity host, including the host, the ligand, and all water molecules within 4.5 Å of the ligand in the QM calculations (158–224 atoms). We use single-step exponential averaging (ssEA) and the non-Boltzmann Bennett acceptance ratio (NBB) methods to estimate QM/MM free energy with the semi-empirical PM6-DH2X method, both based on interaction energies.

QM and QM/MM

A simple graphical approach to predict local residue conformation using NMR chemical shifts and density functional theory

Hooria Shaghghi [University of Pennsylvania], Hossein Pasha Ebrahimi, Fariba Fathi, Niloufar Bahrami Panah, Mehdi Jalali-Heravi and Mohsen Tafazzoli

J. Comp. Chem., **37**, 1296–1305, 2016.

The dependency of amino acid chemical shifts on ϕ and ψ torsion angle is, independently, studied using a five-residue fragment of ubiquitin and ONIOM(DFT:HF) approach. The variation of absolute deviation of $^{13}\text{C}^\alpha$ chemical shifts relative to ϕ dihedral angle is specifically dependent on secondary structure of protein not on amino acid type and fragment sequence. This dependency is observed neither on any of $^{13}\text{C}^\beta$, and $^1\text{H}^\alpha$ chemical shifts nor on the variation of absolute deviation of $^{13}\text{C}^\alpha$ chemical shifts relative to ψ dihedral angle.

QM and QM/MM (Cont'd)

Quantum chemical study on the stability of honeybee queen pheromone against atmospheric factors

Rongwei Shi [Hefei Institutes of Physical Science], Fanglin Liu

J. Mol.Mod., **22**, 140, 2016.

The managed honeybee, *Apis mellifera*, has been experienced a puzzling event, termed as colony collapse disorder (CCD), in which worker bees abruptly disappear from their hives. Potential factors include parasites, pesticides, malnutrition, and environmental stresses. However, so far, no definitive relationship has been established between specific causal factors and CCD events. Here we theoretically test whether atmospheric environment could disturb the chemical communication between the queen and their workers in a colony.

Ligand Docking

Investigation on critical structural motifs of ligands for triggering glucocorticoid receptor nuclear migration through molecular docking simulations

Ya-Lin Liu [National Chung Hsing University], Soonmin Jang, Shih-Min Wang, Chiu-Hao Chen & Feng-Yin Li

J. Biomol. Stru. and Dyn., **34**, 1214-1231, 2016.

The glucocorticoid receptor (GR), a transcription factor regulating gene expression in a ligand-dependent fashion, is known for flexibility in adapting various ligands with their structures ranging from steroid to non-steroid. However, in our previous study, GR shows a stringent discrimination against a set of steroid ligands with highly similar structures for triggering its nuclear migration. In order to resolve this puzzle, we employed molecular docking simulations to investigate the origin of this structural discrimination.

Docking Screens for Novel Ligands Conferring New Biology

John J. Irwin [University of California—San Francisco] and Brian K. Shoichet

Jou. Med. Chem., **59**, 4103–4120, 2016.

It is now plausible to dock libraries of 10 million molecules against targets over several days or weeks. When the molecules screened are commercially available, they may be rapidly tested to find new leads. Although docking retains important liabilities (it cannot calculate affinities accurately nor even reliably rank order high-scoring molecules), it can often distinguish likely from unlikely ligands, often with hit rates above 10%. Here we summarize the improvements in libraries, target quality, and methods that have supported these advances, and the open access resources that make docking accessible.

OpenGrowth: An Automated and Rational Algorithm for Finding New Protein Ligands

Nicolas Chéron, Naveen Jasty, and Eugene I. Shakhnovich [Harvard University, Cambridge]

Jou. Med. Chem., **59**, 4171–4188, 2016.

We present a new open-source software, called OpenGrowth, which aims to create de novo ligands by connecting small organic fragments in the active site of proteins. Molecule growth is biased to produce structures that statistically resemble drugs in an input training database. Consequently, the produced molecules have superior synthetic accessibility and pharmacokinetic properties compared with randomly grown molecules. The growth process can take into account the flexibility of the target protein and can be started from a seed to mimic R-group strategy or fragment-based drug discovery.

Ligand Docking (Cont'd)

WScore: A Flexible and Accurate Treatment of Explicit Water Molecules in Ligand–Receptor Docking

Robert B. Murphy, Matthew P. Repasky, Jeremy R. Greenwood, Ivan Tubert-Brohman, Steven Jerome, Ramakrishna Annabhimoju, Nicholas A. Boyles, Christopher D. Schmitz, Robert Abel, Ramy Farid, and Richard A. Friesner [Columbia University, New York]

Jou. Med. Chem., **59**, 4364–4384, 2016.

We have developed a new methodology for protein–ligand docking and scoring, WScore, incorporating a flexible description of explicit water molecules. The locations and thermodynamics of the waters are derived from a WaterMap molecular dynamics simulation. The water structure is employed to provide an atomic level description of ligand and protein desolvation. WScore also contains a detailed model for localized ligand and protein strain energy and integrates an MM-GBSA scoring component with these terms to assess delocalized strain of the complex.

Application of the quantum mechanical IEF/PCM-MST hydrophobic descriptors to selectivity in ligand binding

Tiziana Ginex, Jordi Muñoz-Muriedas, Enric Herrero, Enric Gibert, Pietro Cozzini, F. Javier Luque [University of Barcelona]

J. Mol.Mod., **22**, 136, 2016.

We have recently reported the development and validation of quantum mechanical (QM)-based hydrophobic descriptors derived from the parametrized IEF/PCM-MST continuum solvation model for 3D-QSAR studies within the framework of the Hydrophobic Pharmacophore (HyPhar) method. In this study we explore the applicability of these descriptors to the analysis of selectivity fields. To this end, we have examined a series of 88 compounds with inhibitory activities against thrombin, trypsin and factor Xa, and the HyPhar results have been compared with 3D-QSAR models reported in the literature.

A Hybrid Approach to Structure and Function Modeling of G Protein-Coupled Receptors

Dorota Latek, Marek Bajda, and Sławomir Filipek [University of Warsaw]

J.Chem. Infor. and Mod., **56**, 630–641, 2016.

The recent GPCR Dock 2013 assessment of serotonin receptor 5-HT_{1B} and 5-HT_{2B}, and smoothened receptor SMO targets, exposed the strengths and weaknesses of the currently used computational approaches. In GPCR Dock 2013, accurate prediction of the SMO target was still beyond the capabilities of most research groups. Another bottleneck in the current GPCR research, as demonstrated by the 5-HT_{2B} target, is the reliable prediction of global conformational changes induced by activation of GPCRs. In this work, we report details of our protocol used during GPCR Dock 2013.

GPCR-Bench: A Benchmarking Set and Practitioners' Guide for G Protein-Coupled Receptor Docking

Dahlia R. Weiss, Andrea Bortolato, Benjamin Tehan, and Jonathan S. Mason [Heptares Therapeutics Ltd., BioPark]

J.Chem. Infor. and Mod., **56**, 642–651, 2016.

Virtual screening is routinely used to discover new ligands and in particular new ligand chemotypes for G protein-coupled receptors (GPCRs). To prepare for a virtual screen, we often tailor a docking protocol that will enable us to select the best candidates for further screening. To aid this, we created GPCR-Bench, a publically available docking benchmarking set in the spirit of the DUD and DUD-E reference data sets for validation studies, containing 25 nonredundant high-resolution GPCR costructures with an accompanying set of diverse ligands and computational decoy molecules for each target.

Ligand Docking (Cont'd)

Deciphering the Complexity of Ligand-Protein Recognition Pathways Using Supervised Molecular Dynamics (SuMD) Simulations

Alberto Cuzzolin, Mattia Sturlese, Giuseppe Deganutti, Veronica Salmaso, Davide Sabbadin, Antonella Ciancetta, and Stefano Moro [University of Padova]

J.Chem. Infor. and Mod., **56**, 687–705, 2016.

Molecular recognition is a crucial issue when aiming to interpret the mechanism of known active substances as well as to develop novel active candidates. Unfortunately, simulating the binding process is still a challenging task because it requires classical MD experiments in a long microsecond time scale that are affordable only with a high-level computational capacity. In order to overcome this limiting factor, we have recently implemented an alternative MD approach, named supervised molecular dynamics (SuMD), and successfully applied it to G protein-coupled receptors (GPCRs).

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 66, May, 2016.

- 1-8 **Application of DPD in the design of polymeric nano-micelles as drug carriers**, Mohammad Ramezani, Jamal Shamsara [Mashhad University of Medical Sciences]

Developing new drug carrier systems are of a great importance in the treatment approach for a wide range of diseases. The simulation techniques can be valuable for decreasing the time and cost of developing novel drug carriers. Among the simulation methods there are a vast number of studies using dissipative particle dynamics (DPD) method for the prediction of different aspects of polymeric nano-micelles for encapsulating drugs. Here, we reviewed the results of the studies employing DPD for the simulation of drug loading and release in different polymeric micelles carriers.

- 9-19 **Effect of temperature on the structure and hydration layer of TATA-box DNA: A molecular dynamics simulation study**, Sudipta Samanta [Massachusetts Institute of Technology, Cambridge], Devanathan Raghunathan, Sanchita Mukherjee

See Applications / Nucleic Acids.

- 20-25 **Charge-tunable insertion process of carbon nanotubes into DNA nanotubes**, Lijun Liang, Zhisen Zhang, Zhe Kong, Yong Liu, Jia-Wei Shen, Debing Li, Qi Wang [Zhejiang University]

See Applications / Carbon Nanotubes.

- 26-40 **Ole e 13 is the unique food allergen in olive: Structure-functional, substrates docking, and molecular allergenicity comparative analysis**, J.C. Jimenez-Lopez [Spanish National Research Council], P. Robles-Bolivar, F.J. Lopez-Valverde, E. Lima-Cabello, S.O. Kotchoni, J.D. Alché

See Applications / Medicinal Chemistry and Drug Design.

- 41-46 **Theoretical Study on Free Fatty Acid Elimination Mechanism for Waste Cooking Oils to Biodiesel over Acid Catalyst**, Kai Wang, Xiaochao Zhang, Jilong Zhang, Zhiqiang Zhang, Caimei Fan [Taiyuan University of Technology], Peide Han

A theoretical investigation on the esterification mechanism of free fatty acid (FFA) in waste cooking oils (WCOs) has been carried out using DMol³ module based on the density functional theory (DFT). Three potential pathways of FFA esterification reaction are designed to achieve the formation of fatty acid methyl ester (FAME), and calculated results show that the energy barrier can be efficiently reduced from 88.597 kcal/mol to 15.318 kcal/mol by acid catalyst.

- 47-57 **Using DFT methodology for more reliable predictive models: Design of inhibitors of Golgi α -Mannosidase II**, Adela Bobovská, Igor Tvaroška, Juraj Kóna [Slovak Academy of Sciences]

See Methodology / QSAR.

- 58-66 **DFT study of the chlorine promotion effect on the ethylene adsorption over iron clusters**, Farideh Pahlavan, Ali H. Pakiari [Shiraz University]

This work explores how electronic perturbations induced by chlorine atoms can enhance the activity of iron toward ethylene. The metal clusters include Fe_n ($n = 2-4$), in which each adatom (Cl) has an inclination to be adsorbed at the bridge site with electrostatic interaction.

- 67-75 **In-silico bonding schemes to encode chemical bonds involving sharing of electrons in molecular structures**, Sankar Punnaivanam [Pondicherry Engineering College], Jerome Pastal Raj Sathiadhas, Vinoth Panneerselvam

Encoding of covalent and coordinate covalent bonds in molecular structures using ground state valence electronic configuration is achieved. The bonding due to electron sharing in the molecular structures is described with five fundamental bonding categories viz. uPair-uPair, lPair-uPair, uPair-lPair, vPair-lPair, and lPair-lPair.

- 76-84 **Tautomeric transformation of temozolomide, their proton affinities and chemical reactivities: A theoretical approach**, Wichien Sang-aroon [Rajamangala University of Technology Isan], Vithaya Ruangpornvisuti, Vittaya Amornkitbamrung

The gas-phase geometry optimizations of bare, mono- and dihydrated complexes of temozolomide isomers were carried out using density functional calculation at the M06 - 2X/6 - 31 + G(d,p) level of the theory.

- 85-90 **Graphene confinement effects on melting/freezing point and structure and dynamics behavior of water**, Masumeh Foroutan [University of Tehran, Tehran], S. Mahmood Fatemi, F. Shokouh

In this work, the melting/freezing point of confined water between two graphene sheets was calculated from the direct coexistence of the solid-liquid interface. Also, molecular dynamics simulation of confined liquid water-ice between two graphene sheets was applied.

- 91-98 **Towards accurate porosity descriptors based on guest-host interactions**, Dooam Paik, Maciej Haranczyk, Jihan Kim [KAIST, 291 Daehak-ro, Yuseong-gu]

For nanoporous materials at the characterization level, geometry-based approaches have become the methods of choice to provide information, often encoded in numerical descriptors, about the pores and the channels of a porous material. In this work, we revisit and quantify the shortcoming of the geometry-based approaches.

- 99-107 **Virtual screening of eighteen million compounds against dengue virus: Combined molecular docking and molecular dynamics simulations study**, Shaher Bano Mirza, Ramin Ekhteiari Salmas, M. Qaiser Fatmi, Serdar Durdagi [Bahcesehir University]

See Applications / Medicinal Chemistry and Drug Design.

- 108-114 **Investigating the importance of Delaunay-based definition of atomic interactions in scoring of protein-protein docking results**, Rahim Jafari [Tarbiat Modares University], Mehdi Sadeghi, Mehdi Mirzaie

See Applications / Protein-Protein Interactions.

- 115-122 **Homology modeling and molecular docking studies of Drosophila and Aedes sex peptide receptors**, Jeong-hyun Kim, Soo-Kyung Kim, Jae-Hyuk Lee, Young-Joon Kim, William A. Goddard III, Yong-Chul Kim [Gwangju Institute of Science and Technology]

See Applications / Homology Modeling.

- 123-132 **Interactions between pyrazole derived enantiomers and Chiralcel OJ: Prediction of enantiomer absolute configurations and elution order by molecular dynamics simulations**, Guixiang Hu, Meilan Huang [Queen's University Belfast], Chengcai Luo, Qi Wang, Jian-Wei Zou

See Applications / Medicinal Chemistry and Drug Design.

- 133-142 **Structure-based designing of sordarin derivative as potential fungicide with pan-fungal activity**, Biprashekhar Chakraborty, Nikunj Kumar Vinodray Sejal, Pavan V. Payghan, Nanda Ghoshal, Jayati Sengupta [Indian Institute of Chemical Biology]

Fungal infections have become a significant problem for immunosuppressed patients. Sordarin, a promising fungicidal agent, inhibits fungal protein synthesis by impairing elongation factor-2 (eEF2) function. We aimed for computer-aided designing of sordarin derivatives as potential fungicidal agents that still remain ineffective against human eEF2.

- 143-154 **Fragment oriented molecular shapes**, Ethan Hain, Carlos J. Camacho, David Ryan Koes [University of Pittsburgh]

Molecular shape is an important concept in drug design and virtual screening. Shape similarity typically uses either alignment methods, which dynamically optimize molecular poses with respect to the query molecular shape, or feature vector methods, which are computationally less demanding but less accurate. The computational cost of alignment can be reduced by pre-aligning shapes, as is done with the Volumetric-Aligned Molecular Shapes (VAMS) method. Here, we introduce and evaluate fragment oriented molecular shapes (FOMS), where shapes are aligned based on molecular fragments.

- 155-167 **Determination of the protonation state for the catalytic dyad in β -secretase when bound to hydroxyethylamine transition state analogue inhibitors: A molecular dynamics simulation study**, Carlos Gueto-Tettay [Universidad de Cartagena], Roberto Pestana-Nobles, Juan Carlos Drosos-Ramirez

See Applications / Enzyme Catalysis.

- 168-173 **CTViz: A tool for the visualization of transport in nanocomposites**, Benjamin Beach, Joshua Brown, Taylor Tarlton, Pedro A. Derosa [Louisiana Tech University]

A visualization tool (CTViz) for charge transport processes in 3-D hybrid materials (nanocomposites) was developed, inspired by the need for a graphical application to assist in code debugging and data presentation of an existing in-house code.

- 174-186 **Docking, QM/MM, and molecular dynamics simulations of the hexose transporter from Plasmodium falciparum (PfHT)**, Amanda Luisa da Fonseca [Universidade Federal de São João del-Rei], Renata Rachide Nunes, Vanildo Martins Lima Braga, Moacyr Comar Jr, Ricardo José Alves, Fernando de Pilla Varotti, Alex Gutterres Taranto

See Methodology / QM and QM/MM.

- 187-195 **Tuning of the stability and energy levels of singlet exciton fission relevant excited states of pentacenes by site-specific substitution**, Li Shen, Yuhan Chen, Xiyu Li [Xinjiang Technical Institute of Physics & Chemistry], Chungang Li

Pentacene crystals or oligomers undergo efficient singlet exciton fission (SF) after photo-excitation, which is expected to be useful in overcoming the Shockley-Queisser theoretical limit of solar cells. However, pentacenes are extremely unstable in air due to oxidation by oxygen. In this work, we designed a group of pentacene compounds with different substituents at different positions.

- 196-200 **CO oxidation catalyzed by silicon carbide (SiC) monolayer: A theoretical study**, Nan Wang, Yu Tian, Jingxiang Zhao, Peng Jin [Hebei University of Technology]

Developing metal-free catalysts for CO oxidation has been a key scientific issue in solving the growing environmental problems caused by CO emission. In this work, the potential of the silicon carbide (SiC) monolayer as a metal-free catalyst for CO oxidation was systematically explored by means of density functional theory (DFT) computations.

Journal of Computational Chemistry, 37 (13), May, 2016.

- 1139-1146 **A method for predicting protein conformational pathways by using molecular dynamics simulations guided by difference distance matrices**, Yasushige Yonezawa [Kinki University]

See Applications / Protein Conformational Analysis.

- 1147-1162 **Development and validation of hydrophobic molecular fields derived from the quantum mechanical IEF/PCM-MST solvation models in 3D-QSAR**, Tiziana Ginex, Jordi Muñoz-Muriedas, Enric Herrero, Enric Gibert, Pietro Cozzini and F. J. Luque [University of Barcelona]

See Methodology / QSAR.

- 1163-1174 **Combined QM(DFT)/MM molecular dynamics simulations of the deamination of cytosine by yeast cytosine deaminase (yCD)**, Xin Zhang, Yuan Zhao, Honggao Yan, Zexing Cao and Yirong Mo [Western Michigan University]

See Applications / Enzyme Catalysis.

- 1175-1190 **Improving B3LYP heats of formation with three-dimensional molecular descriptors**, Yuwei Zhou, Jianming Wu and Xin Xu [Fudan University]

In the present work, we propose the X_{3D} method that extends the B3LYP method by correcting its errors on heats of formation of hydrocarbons (HCs) with three-dimensional (3D) molecular descriptors.

- 1191-1205 **Automatic molecular structure perception for the universal force field**, Svetlana Artemova, Léonard Jaillet and Stephane Redon [University Grenoble Alpes]

The Universal Force Field (UFF) is a classical force field applicable to almost all atom types of the periodic table. Such a flexibility makes this force field a potential good candidate for simulations involving a large spectrum of systems and, indeed, UFF has been applied to various families of molecules.

- 1206–1213 **Structure and electrochemical properties for complexes of nitrocompounds with inorganic ions: A theoretical approach**, Liudmyla K. Sviatenko, Leonid Gorb, Frances C. Hill, Danuta Leszczynska and Jerzy Leszczynski [Jackson State University]

Reduction and oxidation (redox) reactions are widely used for removal of nitrocompounds from contaminated soil and water. Structures and redox properties for complexes of nitrocompounds, such as 2,4,6-trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), 2,4-dinitroanisole (DNAN), and 5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one (NTO), with common inorganic ions (Na^+ , Cl^- , NO_3^-) were investigated at the SMD(Pauling)/PCM(Pauling)/MPWB1K/TZVP level of theory.

- 1214–1222 **A genetic algorithm encoded with the structural information of amino acids and dipeptides for efficient conformational searches of oligopeptides**, Xiao Ru, Ce Song and Zijing Lin [University of Science and Technology of China]

See Applications / Protein Conformational Analysis.

- 1223–1229 **Sequence-based prediction of protein–peptide binding sites using support vector machine**, Ghazaleh Taherzadeh, Yuedong Yang, Tuo Zhang, Alan Wee-Chung Liew and Yaoqi Zhou [Griffith University, Southport]

See Applications / Protein-Protein Interactions.

Journal of Computational Chemistry, 37 (14), May, 2016.

- 1251–1258 **Inherent structure versus geometric metric for state space discretization**, Hanzhong Liu, Minghai Li, Jue Fan and Shuanghong Huo [Gustaf H. Carlson School of Chemistry and Biochemistry]

Inherent structure (IS) and geometry-based clustering methods are commonly used for analyzing molecular dynamics trajectories. ISs are obtained by minimizing the sampled conformations into local minima on potential/effective energy surface. We investigate the influence of the applications of these two methods of trajectory decomposition on our understanding of the thermodynamics and kinetics of alanine tetrapeptide.

- 1259–1264 **Trimeric cluster of lithium amidoborane—the smallest unit for the modeling of hydrogen release mechanism**, Anna V. Pomogaeva [St. Petersburg State University], Keiji Morokuma and Alexey Y. Timoshkin

A detailed first-principle DFT M06/6-311++G(d,p) study of dehydrogenation mechanism of trimeric cluster of lithium amidoborane is presented. The first step of the reaction is association of two LiNH_2BH_3 molecules in the cluster.

- 1265–1273 **Interplay between aromaticity and strain in double group transfer reactions to 1,2-benzynes**, Israel Fernández and Fernando P. Cossío [Universidad Del País Vasco-Euskal Herriko Unibertsitatea]

Density Functional Theory calculations are used to explore the double hydrogen atom transfer from different alkanes to 1,2-benzynes.

- 1274–1282 **A new approach for second-order perturbation theory**, David G. Tomlinson, Andrey Asadchev and Mark S. Gordon [Iowa State University, Ames]

A new second-order perturbation theory (MP2) approach is presented for closed shell energy evaluations. The new algorithm has a significantly lower memory footprint, a lower FLOP (floating point operations) count, and a lower time to solution compared to previously implemented parallel MP2 methods in the GAMESS software package.

- 1283–1295 **Flexibility–rigidity index for protein–nucleic acid flexibility and fluctuation analysis**, Kristopher Opron, Kelin Xia, Zach Burton and Guo-Wei Wei [The Ohio State University]

See Applications / Protein-Nucleic acids.

- 1296–1305 **A simple graphical approach to predict local residue conformation using NMR chemical shifts and density functional theory**, Hooria Shaghghi [University of Pennsylvania], Hossein Pasha Ebrahimi, Fariba Fathi, Niloufar Bahrami Panah, Mehdi Jalali-Heravi and Mohsen Tafazzoli

See Methodology / QM and QM/MM.

- 1306–1312 **Performance of the OP correlation functional in relation to its formulation: Influence of the exchange component and the effect of incorporating same-spin correlations**, Bun Chan [University of Sydney], Jong-Won Song, Yukio Kawashima and Kimihiko Hirao

In the present study, we have investigated two significant features of the OP correlation functional, namely the incorporation of the exchange functional into itself, and the inclusion of only opposite-spin (OS) effects.

- 1313–1320 **Curvature-dependent adsorption of water inside and outside armchair carbon nanotubes**, Shulai Lei [Freie Universität Berlin], Beate Paulus, Shujuan Li and Burkhard Schmidt

See Applications / Carbon Nanotubes.

- 1321–1327 **Comparative studies on group III σ -hole and π -hole interactions**, Lei Gao, Yanli Zeng, Xueying Zhang and Lingpeng Meng [Hebei Normal University]

The σ -hole of M_2H_6 ($M = Al, Ga, In$) and π -hole of MH_3 ($M = Al, Ga, In$) were discovered and analyzed, the bimolecular complexes $M_2H_6 \cdots NH_3$ and $MH_3 \cdots N_2P_2F_4$ ($M = Al, Ga, In$) were constructed to carry out comparative studies on the group III σ -hole interactions and π -hole interactions.

Journal of Computational Chemistry, 37 (15), June, 2016.

- 1335–1344 **A theoretical description of charge reorganization energies in molecular organic P-type semiconductors**, Charlotte Brückner and Bernd Engels [Institut für Physikalische und Theoretische Chemie]

Charge transport properties of materials composed of small organic molecules are important for numerous optoelectronic applications. A material's ability to transport charges is considerably influenced by the charge reorganization energies of the composing molecules. Hence, predictions about charge-transport properties of organic materials deserve reliable statements about these charge reorganization energies.

- 1345–1354 **Scrutinizing “Invisible” astatine: A challenge for modern density functionals**, Dumitru-Claudiu Sergentu, Grégoire David, Gilles Montavon, Rémi Maurice and Nicolas Galland [Université De Nantes]

The main-group 6p elements did not receive much attention in the development of recent density functionals. In many cases it is still difficult to choose among the modern ones a relevant functional for various applications. Here, we illustrate the case of astatine species (At, $Z=85$) and we report the first, and quite complete, benchmark study on several properties concerning such species.

- 1355–1362 **Complexes of adamantane-based group 13 Lewis acids and superacids: Bonding analysis and thermodynamics of hydrogen splitting**, Majid El-Hamdi, Miquel Solà, Jordi Poater and Alexey Y. Timoshkin [St. Petersburg State University]

The electronic structure and chemical bonding in donor–acceptor complexes formed by group 13 element adamantane and perfluorinated adamantane derivatives $EC_9R'_{15}$ ($E = B, Al$; $R' = H, F$) with Lewis bases XR_3 and XC_9H_{15} ($X = N, P$; $R = H, CH_3$) have been studied using energy decomposition analysis at the BP86/TZ2P level of theory.

- 1363–1366 **Regioselective multistep reconstructions of half-saturated zigzag carbon nanotubes**, Wei-Wei Wang, Jing-Shuang Dang, Xiang Zhao and Shigeru Nagase [Fukui Institute for Fundamental Chemistry]

The open edge reconstruction of half-saturated (6,0) zigzag carbon nanotube (CNT) was introduced by density functional calculations. The multistep rearrangement was demonstrated as a regioselective process to generate a defective edge with alternating pentagons and heptagons.

- 1367–1372 **First example of the correlated calculation of the one-bond tellurium–carbon spin–spin coupling constants: Relativistic effects, vibrational corrections, and solvent effects**, Irina L. Rusakova [Siberian Branch of the Russian Academy of Sciences], Yury Yu. Rusakov and Leonid B. Krivdin

This work reports on the comprehensive calculation of the NMR one-bond spin–spin coupling constants (SSCCs) involving carbon and tellurium, $^1J(^{125}\text{Te}, ^{13}\text{C})$, in four representative compounds: $\text{Te}(\text{CH}_3)_2$, $\text{Te}(\text{CF}_3)_2$, $\text{Te}(\text{C}\equiv\text{CH})_2$, and tellurophene.

- 1373–1387 **Interacting quantum fragments-rooted preorganized-interacting fragments attributed relative molecular stability of the Be^{II} complexes of nitrilotriacetic acid and nitrilotri-3-propionic acid**, Ignacy Cukrowski [University of Pretoria, Hatfield] and Paidamwoyo Mangondo

A method designed to investigate, on a fundamental level, the origin of relative stability of molecular systems using Be^{II} complexes with nitrilotriacetic acid (NTA) and nitrilotri-3-propionic acid (NTPA) is described.

- 1388–1395 **Electron tunneling in proteins program**, Muhammad A. Hagra and Alexei A. Stuchebrukhov [University of California, Davis]

See Applications / Bioinformatics.

- 1396–1405 **Theoretical estimation of the rate of photoinduced charge transfer reactions in triphenylamine C₆₀ donor–acceptor conjugate**, Juan Pablo Martínez, Miquel Solà and Alexander A. Voityuk [Institució Catalana de Recerca i Estudis Avançats (ICREA)]

Fullerene-based molecular heterojunctions such as the [6,6]-pyrrolidine-C₆₀ donor–acceptor conjugate containing triphenylamine (TPA) are potential materials for high-efficient dye-sensitized solar cells. In this work, we estimate the rate constants for the photoinduced charge separation and charge recombination processes in TPA-C₆₀ using the unrestricted and time-dependent DFT methods.

Journal of Computational Chemistry, 37 (16), June, 2016.

- 1413–1424 **Sampling free energy surfaces as slices by combining umbrella sampling and metadynamics**, Shalini Awasthi, Venkat Kapil and Nisanth N. Nair [Indian Institute of Technology Kanpur]

Metadynamics (MTD) is a very powerful technique to sample high-dimensional free energy landscapes, and due to its self-guiding property, the method has been successful in studying complex reactions and conformational changes. We combine the standard Umbrella Sampling (US) technique with MTD to sample orthogonal collective variables (CVs) in a simultaneous way.

- 1425–1441 **Highly efficient implementation of pseudospectral time-dependent density-functional theory for the calculation of excitation energies of large molecules**, Yixiang Cao, Thomas Hughes, Dave Giesen, Mathew D. Halls, Alexander Goldberg, Tati Reddy Vadicherla, Madhavi Sastry, Bhargav Patel, Woody Sherman, Andrew L. Weisman and Richard A. Friesner [Columbia University, New York]

We have developed and implemented pseudospectral time-dependent density-functional theory (TDDFT) in the quantum mechanics package Jaguar to calculate restricted singlet and restricted triplet, as well as unrestricted excitation energies with either full linear response (FLR) or the Tamm–Dancoff approximation (TDA) with the pseudospectral length scales, pseudospectral atomic corrections, and pseudospectral multigrid strategy included in the implementations to improve the chemical accuracy and to speed the pseudospectral calculations.

- 1442–1450 **Temperature dependence of strain energy and thermodynamic properties of V₂O₅-based single-walled nanotubes: Zone-folding approach**, Vitaly V. Porsev, Andrei V. Bandura and Robert A. Evarestov [St. Petersburg State University]

A zone-folding approach is applied to estimate the thermodynamic properties of V₂O₅-based nanotubes. The results obtained are compared with those from the direct calculations. It is shown that the zone-folding approximation allows an accurate estimation of nanotube thermodynamic properties and gives a gain in computation time compared to their direct calculations.

- 1451–1462 **Relationship between orbital energy gaps and excitation energies for long-chain systems**, Takao Tsuneda [University of Yamanashi], Raman K. Singh and Ayako Nakata

The difference between the excitation energies and corresponding orbital energy gaps, the exciton binding energy, is investigated based on time-dependent (TD) density functional theory (DFT) for long-chain systems: all-trans polyacetylenes and linear oligoacenes. The optimized geometries of these systems indicate that bond length alternations significantly depend on long-range exchange interactions.

- 1463–1475 **Energy transfer dynamics and kinetics of elementary processes (promoted) by gas-phase CO₂-N₂ collisions: Selectivity control by the anisotropy of the interaction**, Andrea Lombardi, Fernando Pirani, Antonio Laganà and Massimiliano Bartolomei [Università di Perugia]

In this work, we exploit a new formulation of the potential energy and of the related computational procedures, which embodies the coupling between the intra and intermolecular components, to characterize possible propensities of the collision dynamics in energy transfer processes of interest for simulation and control of phenomena occurring in a variety of equilibrium and nonequilibrium environments.

- 1476–1483 **A new method applicable to study solid compounds with multiple polyhedral structures**, Zhenlian Chen and Jun Li [Chinese Academy of Sciences, Ningbo]

A new direct summation method, named as polyhedron method, is proposed to calculate Madelung energy. This method calculates sums of electrostatic interactions over sets of neutral polyhedron unit pairs rather than conventional ion pairs; this gives Madelung constant in a matrix.

- 1484–1490 **Theoretical strategies toward stabilization of singlet remote N-heterocyclic carbenes**, Bitupon Borthakur, Bernard Silvi, Rian D. Dewhurst and Ashwini K. Phukan [Tezpur University, Napaam]

Theoretical investigations predict that the singlet states of ylide-substituted remote carbenes are significantly stable and comparable to those of experimentally known NHCs. They are also found to be strongly σ -donating in nature as evident from an evaluation of the carbonyl stretching frequencies (ν_{CO}) of their complexes with the [Rh(CO)₂Cl] fragment.

Journal of Computational Chemistry, 37 (17), June, 2016.

- 1531–1536 **Quantum monte carlo study of the energetics of small hydrogenated and fluoride lithium clusters**, N. L. Moreira, B. G. A. Brito, J. N. Teixeira Rabelo and Ladir Cândido [Universidade Federal de Goiás - UFG]

An investigation of the energetics of small lithium clusters doped either with a hydrogen or with a fluorine atom as a function of the number of lithium atoms using fixed-node diffusion quantum Monte Carlo (DMC) simulation is reported.

- 1537–1551 **SOP-GPU: influence of solvent-induced hydrodynamic interactions on dynamic structural transitions in protein assemblies**, Andrey Alekseenko, Olga Kononova, Yaroslav Kholodov, Kenneth A. Marx and Valeri Barsegov [University of Massachusetts]

See Applications / Protein Dynamics.

- 1552–1558 **Computational study of basis set and electron correlation effects on anapole magnetizabilities of chiral molecules**, Natalia Zarycz, Patricio F. Provasi, Gabriel I. Pagola, Marta B. Ferraro, Stefano Pelloni and Paolo Lazzeretti [Università degli Studi di Modena e Reggio Emilia]

In the presence of a static, nonhomogeneous magnetic field, represented by the axial vector $\mathbf{B}$ at the origin of the coordinate system and by the polar vector $\mathbf{C}=\mathbf{V}\times\mathbf{B}$, assumed to be spatially uniform, the chiral molecules investigated in this paper carry an orbital electronic anapole, described by the polar vector $\mathbf{A}$.

- 1559–1564 **SM-TF: A structural database of small molecule-transcription factor complexes**, Xianjin Xu, Zhiwei Ma, Hongmin Sun and Xiaoqin Zou [University of Missouri]

Transcription factors (TFs) are the proteins involved in the transcription process, ensuring the correct expression of specific genes. Numerous diseases arise from the dysfunction of specific TFs. In fact, over 30 TFs have been identified as therapeutic targets of about 9% of the approved drugs. In this study, we created a structural database of small molecule-transcription factor (SM-TF) complexes, available online at <http://zoulab.dalton.missouri.edu/SM-TF>.

- 1565–1575 **Walking freely in the energy and temperature space by the modified replica exchange molecular dynamics method**, Changjun Chen [Huazhong University of Science and Technology] and Yanzhao Huang

Replica Exchange Molecular Dynamics (REMD) method is a powerful sampling tool in molecular simulations. Recently, we made a modification to the standard REMD method. It places some inactive replicas at different temperatures as well as the active replicas. The method completely decouples the number of the active replicas and the number of the temperature levels. In this article, we make a further modification to our previous method.

- 1576–1588 **Reparameterizations of the χ Torsion and Lennard-Jones σ Parameters Improve the Conformational Characteristics of Modified Uridines**, Indrajit Deb, Rupak Pal, Joanna Sarzynska and Ansuman Lahiri [University of Calcutta, Kolkata]

See Methodology / Potentials and Parameters.

- 1589–1600 **Converging ligand-binding free energies obtained with free-energy perturbations at the quantum mechanical level**, Martin A. Olsson, Pär Söderhjelm and Ulf Ryde [Lund University]

See Methodology / Free Energy Perturbations.

- 1601–1610 **Influence of a polarizable surrounding on the electronically excited states of aggregated perylene materials**, Daniel Bellinger, Volker Settels, Wenlan Liu, Reinhold F. Fink and Bernd Engels [Institut für Physikalische und Theoretische Chemie]

To tune the efficiency of organic semiconductor devices it is important to understand limiting factors as trapping mechanisms for excitons or charges. An understanding of such mechanisms deserves an accurate description of the involved electronic states in the given environment. In this study, we investigate how a polarizable surrounding influences the relative positions of electronically excited states of dimers of different perylene dyes.

- 1611–1625 **Hydrogen bonding in the hydroxysulfinyl radical-formic acid-water system: A theoretical study**, Simona Tušar and Antonija Lesar [Jožef Stefan Institute, Ljubljana]

Quantum chemical methods have been employed to evaluate the possible configurations of the 1:1 and 1:2 HOSO-formic acid complexes and 1:1:1 HOSO-formic acid-water complexes. The first type of complex involves two H bonds, while the other two types comprise three H bonds in a ring.

Journal of Molecular Modeling, 22 (5), May, 2016.

- 118 **On the performance of ruthenium dyes in dye sensitized solar cells: a free cluster approach based on theoretical indexes**, M. Barrera [Pontificia Universidad Católica de Chile], I. Crivelli, B. Loeb

The performance of ruthenium dye sensitized solar cells (DSSC) with different types of ligand was studied by means of a theoretical model where the ruthenium complex is bound to two $[\text{Ti}(\text{OH})_3]^+$ units, instead of the more usual cluster TiO_2 model.

- 117 **Theoretical study on the initial reaction mechanisms of ansa-metallocene zirconium precursor on hydroxylated Si(1 0 0) surface**, Guangfen Zhou, Jie Ren [Hebei University of Science and Technology], Shaowen Zhang

The initial reaction mechanisms for depositing ZrO_2 thin films using ansa-metallocene zirconium (Cp_2CMe_2) ZrMe_2 precursor were studied by density functional theory (DFT) calculations.

- 116 **Theoretical study of the regioselective cyclization of enaminones in the construction of benzofurans and indoles**, Rafael Herrera, Francisco Méndez, Fabiola Jiménez, M. Carmen Cruz, Joaquín Tamariz [Escuela Nacional de Ciencias Biológicas]

A theoretical study was undertaken regarding the regioselective Lewis acid-promoted intramolecular cyclization of novel enaminones **1-3** leading to the corresponding benzofurans **4-5** and indoles **6**. The density functional theory (DFT) and hard and soft acids and bases (HSAB) principle provided data to describe the electronic effects of the substituents in the reactivity of the benzene ring and the enaminone moiety.

- 115 **TD-DFT investigation of D- π -A organic dyes with thiophene moieties as π -spacers for use as sensitizers in DSSCs**, Ahmed A. Hasanein [Alexandria University], Yasser R. Elmarassi, Eman N. Kassem

The geometrical, conformational, and electronic properties of a series of D- π -A metal-free dyes designed for use as sensitizers in DSSCs were studied using DFT and TD-DFT methods.

- 114 **Locating structures and evolution pathways of reconstructed rutile $\text{TiO}_2(011)$ using genetic algorithm aided density functional theory calculations**, Pan Ding, Xue-Qing Gong [East China University of Science and Technology]

Titanium dioxide (TiO_2) is an important metal oxide that has been used in many different applications. TiO_2 has also been widely employed as a model system to study basic processes and reactions in surface chemistry and heterogeneous catalysis. In this work, we investigated the (011) surface of rutile TiO_2 by focusing on its reconstruction.

- 113 **Functionalization of fullerene via the Bingel reaction with α -chlorocarbanions: an ONIOM approach**, Nguyen Minh Thong, Thi Chinh Ngo, Duy Quang Dao, Tran Duong, Quoc Tri Tran, Pham Cam Nam [The University of Danang]

Two-layer ONIOM method at the ONIOM(B3LYP/6-31G(d):PM6) level of theory was applied to study the cycloaddition reaction of α -chlorocarbanions (CR_2Cl^- , where R is H, Cl, CH_3 , CN, and NO_2) and fullerene.

- 112 **Non-covalent carriage of anticancer agents by humanized antibody trastuzumab**, Arpita Yadav [Chhatrapati Shahuji Maharaj University], Sweta Sharma, Veejendra Kumar Yadav

This article explores the internalization and non-covalent carriage of small molecule anticancer agents like vinca alkaloids by humanized monoclonal antibody trastuzumab. Such carriage is marked by significant reduction in side effects and increased therapeutic value of these anticancer agents.

- 111 **Applying PyRosetta molecular energies to separate properly oriented protein models from mirror models, obtained from contact maps**, Monika Kurczynska, Ewa Kania, Bogumil M. Konopka, Malgorzata Kotulska [Wroclaw University of Science and Technology]

Reconstructing protein structure based on contact maps leads to two types of models: properly oriented models and mirror models. This is due to the fact that contact maps do not include information on protein chirality. Therefore, both types of model orientations share the same contact map and are geometrically allowed. In this work, we verified the hypothesis that some of the energy terms calculated by PyRosetta could be useful to distinguish between properly oriented and mirror models.

- 110 **Kudi: A free open-source python library for the analysis of properties along reaction paths**, Stefan Vogt-Geisse [Universidad de Concepción]

With increasing computational capabilities, an ever growing amount of data is generated in computational chemistry that contains a vast amount of chemically relevant information. It is therefore imperative to create new computational tools in order to process and extract this data in a sensible way. Kudi is an open source library that aids in the extraction of chemical properties from reaction paths.

- 109 **Improvements in GROMACS plugin for PyMOL including implicit solvent simulations and displaying results of PCA analysis**, Tomasz Makarewicz, Rajmund Kaźmierkiewicz [University of Gdańsk and Medical University of Gdańsk]

See Applications / Bioinformatics.

- 108 **Theoretical insight into the sensitive mechanism of multilayer-shaped cocrystal explosives: compression and slide**, Hong-fei Gao, Shu-hai Zhang [North University of China], Fu-de Ren, Rui-jun Gou, Gang Han, Jing-bo Wu, Xiong Ding, Wen-hu Zhao

Multilayer-shaped compression and slide models were employed to investigate the complex sensitive mechanisms of cocrystal explosives in response to external mechanical stimuli. Here, density functional theory (DFT) calculations implementing the generalized gradient approximation (GGA) of Perdew-Burke-Ernzerhof (PBE) with the Tkatchenko-Scheffler (TS) dispersion correction were applied to a series of cocrystal explosives.

- 107 **Transport properties of simple organic molecules in a transmembrane cyclic peptide nanotube**, Jian Xu, Jian Fen Fan [Soochow University], Ming Ming Zhang, Pei Pei Weng, Hui Fang Lin

Multiple molecular dynamics simulations have been performed to explore the transport properties of single methane, methanol, and ethanol molecules through the water-filled transmembrane cyclic peptide nanotube (CPNT) of 8×(WL-)4-POPE, as well as the potential application of this CPNT in the separation of an alcohol/water mixture.

- 106 **Theoretical investigations on the stability of alkali metal substituted phenylpentazole**, Xueli Zhang, Xuedong Gong [Nanjing University of Science and Technology]

The alkali metal (M=Li, Na, and K) para-substituted (M-1), meta-substituted (M-2) or ortho-substituted (M-3) derivatives of phenylpentazole (PhN₅) were studied using density functional theory.

- 105 **First-principles study of water desorption from montmorillonite surface**, Yao Zhang, Yingfeng Meng, Houbin Liu, Mingli Yang [Sichuan University]

Knowledge about water desorption is important to give a full picture of water diffusion in montmorillonites (MMT), which is a driving factor in MMT swelling. The desorption paths and energetics of water molecules from the surface of MMT with trapped Li⁺, Na⁺ or K⁺ counterions were studied using periodic density functional theory calculations.

- 104 **Deprotonation and acidity characterization of biomass sugars: a first-principles study**, Gang Yang, Chang Zhu, Lijun Zhou [Southwest University, Chongqing]

Deprotonation of biomass sugars is investigated by high-level electronic structure calculations, considering α - and β -anomers as well as all O and C sites. Structural alterations are generally focused on the deprotonated sites.

- 103 **Exploring the cocrystallization potential of urea and benzamide**, Piotr Cysewski [Nicolaus Copernicus University in Toruń], Maciej Przybyłek, Dorota Ziółkowska,

The cocrystallization landscape of benzamide and urea interacting with aliphatic and aromatic carboxylic acids was studied both experimentally and theoretically. Ten new cocrystals of benzamide were synthesized using an oriented samples approach via a fast dropped evaporation technique.

- 101 **DFT studies on the structural and vibrational properties of polyenes**, Teobald Kupka, Aneta Buczek [University of Opole], Małgorzata A. Broda, Michał Stachów, Przemysław Tarnowski

Detailed density functional theory (DFT) calculations on the structure and harmonic frequencies of model all-trans and all-cis polyenes were undertaken.

Journal of Molecular Modeling, 22 (6), June, 2016.

- 140 **Quantum chemical study on the stability of honeybee queen pheromone against atmospheric factors**, Rongwei Shi [Hefei Institutes of Physical Science], Fanglin Liu

See Methodology / QM and QM/MM.

- 139 **Computational investigation of stoichiometric effects, binding site heterogeneities, and selectivities of molecularly imprinted polymers**, Jacob J. Terracina, Magnus Bergkvist [SUNY Polytechnic Institute Colleges of Nanoscale Science and Engineering], Susan T. Sharfstein

A series of quantum mechanical (QM) computational optimizations of molecularly imprinted polymer (MIP) systems were used to determine optimal monomer-to-target ratios. Imidazole- and xanthine-derived target molecules were studied.

- 138 **Thermal reaction of the ionic liquid 1,2-dimethyl-(3-aminoethyl) imidazolium tetrafluoroborate: a kinetic and theoretical study**, Xinming Zhou, Bobo Cao, Shuangyue Liu, Xuejun Sun, Xiao Zhu, Hu Fu [China University of Petroleum]

Since the thermal stabilities of ionic liquids (ILs) are of significance for their application, an amine-functionalized IL 1,2-dimethyl-(3-aminoethyl) imidazolium tetrafluoroborate [aEMMIM][BF₄] was chosen to study thermal decomposition mechanisms via the methods of FT-IR, ¹H NMR, TGA, TGA-MS and density functional theory (DFT) calculations.

- 137 **Theoretical study of the structures and first hyperpolarizabilities of C₆₀Cl_n and Li@C₆₀Cl_n (n = 4, 6, 8, 10)**, Yao-Dong Song, Liang Wang, Li-Ming Wu [Fujian Institute of Research on the Structure of Matter]

We recently reported (Song Y-D et al., 2016, J Mol Model 22:50) that doping with Li greatly affects the static first hyperpolarizability of C₆₀Cl₂. In this work, with a view to creating nonlinear optical materials with high thermodynamic stability and wide transparent regions, a series of Li@C₆₀Cl_n (n = 4, 6, 8, 10) were designed.

- 136 **Application of the quantum mechanical IEF/PCM-MST hydrophobic descriptors to selectivity in ligand binding**, Tiziana Ginex, Jordi Muñoz-Muriedas, Enric Herrero, Enric Gibert, Pietro Cozzini, F. Javier Luque [University of Barcelona]

See Methodology / Ligand Docking.

- 135 **Discovery of ERBB3 inhibitors for non-small cell lung cancer (NSCLC) via virtual screening**, Rong Guo, Yuan Zhang, Xiao Li, Xinrui Song, Da Li, Yong Zhao [Beijing Computing Center]

As a member of the epidermal growth factor receptor family (EGFR) of receptor tyrosine kinases, ERBB3 plays an important role in mediating cellular growth and differentiation. Recent research works identified that CD74-NRG1 fusions lead to overexpression of the EGF-like domain of NRG1, and thus activate ERBB3 and PI3K-AKT signaling pathways. A sequential virtual screening strategy has been applied to ERBB3 crystal structure using databases of natural products and Chinese traditional medicine compounds, and led to identification of a group of small molecular compounds potentially capable of blocking ERBB3. Six small molecular compounds were selected for in vitro analysis.

- 134 **Formation of the Si-B bond: insertion reactions of silylenes into B-X (X = F, Cl, Br, O, and N) bonds**, Bing Geng [University of Jinan], Chongjuan Xu, Zhonghe Chen

The insertion reactions of the silylene H₂Si with H₂BXH_{n-1} (X = F, Cl, Br, O, N; n = 1, 1, 1, 2, 3) have been studied by DFT and MP2 methods.

- 133 **First-principle investigation on growth patterns and properties of cobalt-doped lithium nanoclusters**, Zhenjun Song [South University of Science and Technology of China]

A systematic theoretical investigation on cobalt lithium clusters Li_nCo [1–12] was performed with a DFT approach.

- 132 **QM/MM investigation of the catalytic mechanism of angiotensin-converting enzyme**, Xia Mu, Chunchun Zhang, Dingguo Xu [Sichuan University]

See Applications / Enzyme Catalysis.

- 131 **pH dependence of ligand-induced human epidermal growth factor receptor activation investigated by molecular dynamics simulations**, Jun Dong, Yonghui Zhang, Zhiyong Zhang [Hefei National Laboratory for Physical Science at Microscale and School of Life Sciences]

See Applications / Protein Dynamics.

- 130 **Theoretical study on the substitution reactions of the germolenoid H_2GeLiF with SiH_3X ($\text{X} = \text{F}, \text{Cl}, \text{Br}$)**, Gongxiao Zhang [Taishan Medical University, Taian], Yuhua Qi, Chongjuan Xu

The substitution reactions of H_2GeLiF (**G**) with SiH_3X ($\text{X} = \text{F}, \text{Cl}, \text{Br}$) were investigated using calculations performed at the QCISD/6-311++G (d, p)//B3LYP/6-311+G (d, p) level of theory. The results led to the following conclusions. (i) The substitutions are nucleophilic reactions. There are two substitution paths, I and II, which both lead to the germane $\text{H}_2\text{GeFSiH}_3$.

- 129 **Theoretical studies on a new furazan compound bis[4-nitramino-furazanyl-3-azoxy]azofurazan (ADNAAF)**, Chunmei Zheng, Yuting Chu, Liwen Xu, Fengyun Wang, Wu Lei, Mingzhu Xia, Xuedong Gong [Nanjing University of Science and Technology]

Bis[4-nitraminofurazanyl-3-azoxy]azofurazan (ADNAAF), synthesized in our previous work [1], contains four furazan units connected to the linkage of the azo-group and azoxy-group. For further research, some theoretical characters were studied by the density functional theoretical (DFT) method.

- 128 **Formation of persistent organic pollutants from 2,4,5-trichlorothiophenol combustion: a density functional theory investigation**, Tajwar Dar, Kalpit Shah, Behdad Moghtaderi, Alister J. Page [The University of Newcastle]

Polychlorinated dibenzothiophene (PCDT) and polychlorinated thianthrene (PCTA) are sulfur analogues of dioxins, such as polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/F). In this work, we present a detailed mechanistic and kinetic analysis of PCDT and PCTA formation from the combustion of 2,4,5-trichlorothiophenol.

- 127 **The polythiophene molecular segment as a sensor model for H_2O , HCN , NH_3 , SO_3 , and H_2S : a density functional theory study**, Ali Shokuhi Rad [Islamic Azad University], Mehri Esfahanian, Etesam Ganjian, Habib-allah Tayebi, Samaneh Bagheri Novir

Studying the interaction of some atmospheric gases (H_2O , HCN , NH_3 , SO_3 and H_2S) with 3PT oligomers is important in the development of polymeric sensors for gas detection. In the present study, we studied the relaxed geometries, interaction energies, charge analysis, HOMO–LUMO orbital analysis, and UV–vis spectra of all interacted systems using first-principles density functional theory (DFT).

- 126 **Structure and properties of alizarin complex formed with alkali metal hydroxides in methanol solution**, Tomasz Jeliński [Nicolaus Copernicus University], Piotr Cysewski

Quantum chemical computations were used for prediction of the structure and color of alizarin complex with alkali metal hydroxides in methanolic solutions.

- 125 **Spectroscopic and nonlinear optical properties of new chalcone fluorescent probes for bioimaging applications: a theoretical and experimental study**, Przemysław Krawczyk [Nicolaus Copernicus University], Marek Pietrzak, Tomasz Janek, Beata Jędrzejewska, Piotr Cysewski

In this study, the newly synthesized non-centrosymmetric, 4-dimethylamino-3'-isothiocyanatochalcone (PKA) compound was presented.

- 124 **Cage-like B_{40}^+ : a perfect borospherene monocation**, Hai-Ru Li, Qiang Chen, Xin-Xin Tian, Hai-Gang Lu, Hua-Jin Zhai, Si-Dian Li [Shanxi University, Taiyuan]

The recent discovery of perfect cage-like $D_{2d} B_{40}^-$ and $D_{2d} B_{40}$ (all-boron fullerenes) has led to the emergence of a borospherene family. However, the geometrical and electronic structures of their cationic counterpart B_{40}^+ , previously detected in gas phase, remain unknown to date. Based on extensive first-principles theory calculations, we present herein the possibility of a perfect cage-like $D_{2d} B_{40}^+$ (**1**) ($^2A_1$) for the monocation, which turns out to be the global minimum of the system similar to B_{40}^- and B_{40} , adding a new member to the borospherene family.

- 123 **Theoretical insight into the binding energy and detonation performance of ϵ -, γ -, β -CL-20 cocrystals with β -HMX, FOX-7, and DMF in different molar ratios, as well as electrostatic potential**, Rui-zhi Feng [North University of China, Taiyuan], Shu-hai Zhang, Fu-de Ren, Rui-jun Gou, Li Gao

Molecular dynamics method was employed to study the binding energies on the selected crystal planes of the ϵ -, γ -, β -conformation 2,4,6,8,10,12-hexanitrohexaazaisowurtzitane (ϵ -, γ -, β -CL-20) cocrystal explosives with 1,1-diamino-2,2-dinitroethylene (FOX-7), 1,3,5,7-tetranitro-1,3,5,7-tetrazacyclooctane with β -conformation (β -HMX) and N,N-dimethylformamide (DMF) in different molar ratios.

- 122 **Hydrogenated superalkalis and their possible applications**, Ambrish Kumar Srivastava, Neeraj Misra [University of Lucknow]

Superalkali species possess lower ionization energy than alkali metals, which allow them to form a variety of unusual compounds with interesting properties. Herein, we report the structures and properties of hydrogenated superalkalis (SAHs) such as FLi_2H , OLi_3H , and NLi_4H using ab initio MP2/6-311++G(d,p) level of theory.

- 121 **Does the position of the electron-donating nitrogen atom in the ring system influence the efficiency of a dye-sensitized solar cell? A computational study**, Abul Kalam Biswas, Sunirmal Barik, Amitava Das, Bishwajit Ganguly [Central Salt and Marine Chemicals Research Institute, Bhavnagar]

We have reported a number of new metal-free organic dyes (**2–6**) that have cyclic asymmetric benzotripyrrole derivatives as donor groups with peripheral nitrogen atoms in the ring, fluorine and thiophene groups as π -spacers, and a cyanoacrylic acid acceptor group. Density functional theory (DFT) and time-dependent DFT (TD-DFT) calculations were employed to examine the influence of the position of the donor nitrogen atom and π -conjugation on solar cell performance.

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- 120 **Physical nature of intermolecular interactions inside Sir2 homolog active site: molecular dynamics and ab initio study**, Przemysław Czeleń, Żaneta Czyżnikowska [Wrocław Medical University]

See Applications / Homology Modeling.

- 119 **The nature of inter- and intramolecular interactions in $F_2OXe \cdots HX$ (X= F, Cl, Br, I) complexes**, Emilia Makarewicz, Jan Lundell, Agnieszka J. Gordon, Sławomir Berski [University of Wrocław]

Electronic structure of the $XeOF_2$ molecule and its two complexes with HX (X= F, Cl, Br, I) molecules have been studied in the gas phase using quantum chemical topology methods: topological analysis of electron localization function (ELF), electron density, $\rho(r)$, reduced gradient of electron density $|RDG(r)|$ in real space, and symmetry adapted perturbation theory (SAPT) in the Hilbert space.

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About 105 Papers from more than 30 Journals are cited.

1	APPLICATIONS (73)	Page 2	
1.1	Small Molecules (10)		
	Med. Chem. And Drug Design	Page 2	QSAR Page 4
1.2	Biopolymers (63)		
	Bioinformatics and Cheminformatics	Page 5	Free Energy Calculations Page 11
	Protein Sequence Analysis	Page 6	Ligand Binding Page 11
	Protein Secondary Structure	Page 6	Enzyme Catalysis Page 12
	Protein Structure Prediction	Page 6	Protein-Protein Interactions Page 15
	Comparative or Homology Modeling	Page 7	Membrane Proteins Page 16
	Protein Conformational Analysis	Page 7	Protein Design Page 18
	Protein Structure Analysis	Page 8	Protein Folding Page 18
	Protein Engineering	Page 9	Protein-Nucleic Acids Page 19
	Protein Dynamics	Page 9	Nucleic Acids Page 20
1.3	Polymers		
1.4	Surfaces, Catalysts and Material	Page 21	
2	METHODOLOGY (20)	Page 22	
	QSAR	Page 22	QM & QM/MM Page 24
	Potentials and Parameters	Page 22	Comparative or Homology Page 26
	Molecular Dynamics	Page 23	Ligand Docking Page 26
	Free Energy Perturbation	Page 24	
3	JOURNAL REVIEWS (5)	Page 28	
	Journal of Molecular Graphics and Modeling, 67, June, 2016.		
	Journal of Computational Chemistry, 37 (18, 19, 20), July, 2016.		
	Journal of Molecular Modeling, 22 (7), July, 2016.		
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 38	
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION		

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

DrugE-Rank: improving drug–target interaction prediction of new candidate drugs or targets by ensemble learning to rank

Qingjun Yuan, Junning Gao, Dongliang Wu, Shihua Zhang, Hiroshi Mamitsuka, and Shanfeng Zhu [Fudan University, Shanghai]

Bioinformatics. **32**, i18-i27, 2016.

Identifying drug–target interactions is an important task in drug discovery. To reduce heavy time and financial cost in experimental way, many computational approaches have been proposed. Approaches based on machine learning for this problem can be divided into two types: feature-based and similarity-based methods. We propose a new method, DrugE-Rank, to improve the prediction performance by nicely combining the advantages of the two different types of methods. That is, DrugE-Rank uses LTR, for which multiple well-known similarity-based methods can be used as components of ensemble learning.

Design, biological evaluation and 3D QSAR studies of novel dioxin-containing triaryl pyrazoline derivatives as potential B-Raf inhibitors

Yu-Shun Yang, Bing Yang, Yan Zou, Guigen Li, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med. Chem., **24**, 3052-3061, 2016

A series of novel dioxin-containing triaryl pyrazoline derivatives **C1–C20** have been synthesized. Their B-Raf inhibitory and anti-proliferation activities were evaluated. Compound **C6** displayed the most potent biological activity against B-Raf^{V600E} and WM266.4 human melanoma cell line with corresponding IC₅₀ value of 0.04 μM and GI₅₀ value of 0.87 μM, being comparable with the positive controls and more potent than our previous best compounds. Moreover, **C6** was selective for B-Raf^{V600E} from B-Raf^{WT}, C-Raf and EGFR and low toxic.



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Medicinal Chemistry and Drug Design (Cont'd)

Towards understanding the mechanism of action of antibacterial N-alkyl-3-hydroxypyridinium salts: Biological activities, molecular modeling and QSAR studies

Rafael Dolezal, Ondrej Soukup, David Malinak, Ranylson M.L. Savedra, Jan Marek, Marie Dolezalova, Marketa Pasdiorova, Sarka Salajkova, Jan Korabecny, Jan Honegr, Teodorico C. Ramalho, Kamil Kuca [University Hospital Hradec Kralove]

Eur Jou Med Chem., **121**, 699-711 , 2016.

In this study, we have carried out a combined experimental and computational investigation to elucidate several bred-in-the-bone ideas standing out in rational design of novel cationic surfactants as antibacterial agents. Five 3-hydroxypyridinium salts differing in the length of *N*-alkyl side chain have been synthesized, analyzed by high performance liquid chromatography, tested for *in vitro* activity against a panel of pathogenic bacterial and fungal strains, computationally modeled in water by a SCRf B3LYP/6-311++G(d,p) method, and evaluated by a systematic QSAR analysis.

Pharmacophore model prediction, 3D-QSAR and molecular docking studies on vinyl sulfones targeting Nrf2-mediated gene transcription intended for anti-Parkinson drug design

Mohd Athar, Mohsin Yousuf Lone, Vijay M. Khedkar & Prakash Chandra Jha [Central University of Gujarat]

J. Biomol. Stru. and Dyn., **34**, 1282-1297, 2016.

Despite intense research efforts towards clinical and molecular causes of Parkinson disease (PD), the etiology of disease still remains unclear. However, recent studies have provided ample evidences that the oxidative stress is the key player that contributes a lot to dopaminergic (DAergic) neurodegeneration in brain. In the current study, potent heme oxygenase-1 agonists (Nrf2 signalling regulator), vinyl sulfones, were selected and an optimal pharmacophore model was brought forth which was examined using a decoy set by atom-based 3D-QSAR.

Arylhydrazone derivatives of naproxen as new analgesic and anti-inflammatory agents: Design, synthesis and molecular docking studies

Homa Azizian, Zahra Mousavi, Hamidreza Faraji, Mohammad Tajik, Kowsar Bagherzadeh, Peyman Bayat, Abbas Shafiee, Ali Almasirad [Islamic Azad University]

J. Mol.Graph. and Mod., **66**, 127-136, 2016.

A series of new arylidenehydrazone derivatives of naproxen were synthesized and evaluated for their analgesic and anti-inflammatory activities. Some of the synthesized analogues showed comparable activities when compared against naproxen for their analgesic and anti-inflammatory properties. 2-(6-methoxy-2-naphthyl)-N'-[(pyridine-4-yl)methylene]propanoic acid hydrazide **4j** was found to be the most active analgesic agent. 2-(6-methoxy-2-naphthyl)-N'-[4-nitrobenzylidene]propanoic acid hydrazide **4g** showed highest anti-inflammatory activity in comparison to the naproxen.

Structure-based virtual screening of hypothetical inhibitors of the enzyme longiborneol synthase—a potential target to reduce Fusarium head blight disease

E. Bresso, V. Leroux, M. Urban, K. E. Hammond-Kosack, B. Maigret, N. F. Martins [Biotechnology Parque Estação Biológica - PqEB]

J. Mol.Mod., **22**, 163, 2016.

Fusarium head blight (FHB) is one of the most destructive diseases of wheat and other cereals worldwide. Culmorin possesses a well-known important synergistically virulence role among mycotoxins, and longiborneol synthase appears to be a key enzyme for its synthesis, thus making longiborneol synthase a particularly interesting target. This study aims to discover potent and less toxic agrochemicals against FHB.

Medicinal Chemistry and Drug Design (Cont'd)

Fullerenes and their derivatives as inhibitors of tumor necrosis factor- α with highly promoted affinities

Gaoyin Wu, Xuejiao J. Gao, Joonkyung Jang, Xingfa Gao [Chinese Academy of Sciences]

J. Mol.Mod., **22**, 161, 2016.

Tumor necrosis factor- α (TNF- α) is a cell signalling protein involved in systemic inflammation in infectious and other malignant diseases. Physiologically, it plays an important role in regulating host defence, but its overexpression can lead to serious illnesses including cancer, autoimmune disease and inflammatory disease. In this work, we investigated the inhibiting effects of four types of fullerene-based ligands: fullerenes, fullerlenols, metallofullerenes, and metallofullerenols.

Computational Prediction of HIV-1 Resistance to Protease Inhibitors

Ali Hosseini, Andreu Alibés, Marc Noguera-Julian, Victor Gil, Roger Paredes, Robert Soliva, Modesto Orozco, and Victor Guallar [Barcelona Supercomputing Center]

J.Chem. Infor. and Mod., **56**, 915–923, 2016.

The development of mutations in HIV-1 protease (PR) hinders the activity of antiretroviral drugs, forcing changes in drug prescription. Most resistance assessments used to date rely on expert-based rules on predefined sets of stereotypical mutations; such an information-driven approach cannot capture new polymorphisms or be applied for new drugs. We have created a protocol involving sequence comparison and all-atom protein–ligand induced fit simulations to predict resistance at the molecular level.

Kinetic barriers in the isomerization of substituted ureas: implications for computer-aided drug design

Johannes R. Loeffler, Emanuel S. R. Ehmki, Julian E. Fuchs [University of Innsbruck], Klaus R. Liedl

J.Comp.Aided. Mol.des. **30**, 391-400, 2016.

Urea derivatives are ubiquitously found in many chemical disciplines. N,N'-substituted ureas may show different conformational preferences depending on their substitution pattern. The high energetic barrier for isomerization of the cis and trans state poses additional challenges on computational simulation techniques aiming at a reproduction of the biological properties of urea derivatives. Herein, we investigate energetics of urea conformations and their interconversion using a broad spectrum of methodologies ranging from data mining, via quantum chemistry to molecular dynamics simulation and free energy calculations.

Quantitative Structure-Activity Relations

QSAR analysis of nicotinamidic compounds and design of potential Bruton's tyrosine kinase (Btk) inhibitors

Letícia Santos-Garcia, Letícia C. Assis, Daniela R. Silva, Teodorico C. Ramalho & Elaine F.F. da Cunha [Federal University of Lavras]

J. Biomol. Stru. and Dyn., **34**, 1421-1440, 2016.

Bruton's tyrosine kinase (Btk) is an important enzyme in B-lymphocyte development and differentiation. Furthermore, Btk expression is considered essential for the proliferation and survival of these cells. Btk inhibition has become an attractive strategy for treating autoimmune diseases, B-cell leukemia, and lymphomas. With the objective of proposing new candidates for Btk inhibitors, we applied receptor-dependent four-dimensional quantitative structure–activity relationship (QSAR) methodology to a series of 96 nicotinamide analogs useful as Btk modulators.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SIRAH tools: mapping, backmapping and visualization of coarse-grained models

Matías R. Machado and Sergio Pantano [Institut Pasteur De Montevideo]

Bioinformatics. **32**, 1568-1570, 2016.

Coarse-grained (CG) models reduce the cost of molecular dynamics simulations keeping the essence of molecular interactions. Still, the diversity of CG representations (sizes, connectivity, naming, etc.) hampers the handling and visualization of such models. SIRAH Tools comprises a set of utilities to convert all-atoms coordinates to arbitrary residue-based CG schemes, write GROMACS' topological information at any resolution into PSF format and a VMD plugin to visualize, analyze and retrieve pseudo-atomistic information from CG trajectories performed with the SIRAH force field.

ELASPIC web-server: proteome-wide structure-based prediction of mutation effects on protein stability and binding affinity

Daniel K. Witvliet, Alexey Strokach, Andrés Felipe Giraldo-Forero, Joan Teyra, Recep Colak, and Philip M. Kim [University of Toronto, Toronto]

Bioinformatics. **32**, 1589-1591, 2016.

ELASPIC is a novel ensemble machine-learning approach that predicts the effects of mutations on protein folding and protein-protein interactions. Here, we present the ELASPIC webserver, which makes the ELASPIC pipeline available through a fast and intuitive interface. The webserver can be used to evaluate the effect of mutations on any protein in the Uniprot database, and allows all predicted results, including modeled wild-type and mutated structures, to be managed and viewed online and downloaded if needed.

An algorithm for computing the gene tree probability under the multispecies coalescent and its application in the inference of population tree

Yufeng Wu [University of Connecticut, Storrs]

Bioinformatics. **32**, i225-i233, 2016.

Gene tree represents the evolutionary history of gene lineages that originate from multiple related populations. Under the multispecies coalescent model, lineages may coalesce outside the species (population) boundary. In this article, we present a new algorithm, called CompactCH, for computing the exact gene tree probability. This new algorithm is based on the notion of compact coalescent histories: multiple coalescent histories are represented by a single compact coalescent history.

TargetNet: a web service for predicting potential drug-target interaction profiling via multi-target SAR models

Zhi-Jiang Yao, Jie Dong, Yu-Jing Che, Min-Feng Zhu, Ming Wen, Ning-Ning Wang, Shan Wang, Ai-Ping Lu, Dong-Sheng Cao [Central South University, Changsha]

J.Comp.Aided. Mol.des. **30**, 413-424, 2016.

Drug-target interactions (DTIs) are central to current drug discovery processes and public health fields. Analyzing the DTI profiling of the drugs helps to infer drug indications, adverse drug reactions, drug-drug interactions, and drug mode of actions. Therefore, it is of high importance to reliably and fast predict DTI profiling of the drugs on a genome-scale level. Here, we develop the TargetNet server, which can make real-time DTI predictions based only on molecular structures, following the spirit of multi-target SAR methodology.

Protein Sequence Analysis

DFLpred: High-throughput prediction of disordered flexible linker regions in protein sequences

Fanchi Meng and Lukasz Kurgan [University of Alberta, Edmonton]

Bioinformatics. **32**, i341-i350, 2016.

Disordered flexible linkers (DFLs) are disordered regions that serve as flexible linkers/spacers in multi-domain proteins or between structured constituents in domains. They are different from flexible linkers/residues because they are disordered and longer. We conceptualized, developed and empirically assessed a first-of-its-kind sequence-based predictor of DFLs, DFLpred. This method outputs propensity to form DFLs for each residue in the input sequence. DFLpred uses a small set of empirically selected features that quantify propensities to form certain secondary structures, disordered regions and structured regions, which are processed by a fast linear model.

Protein Secondary Structure

Mechanism of allosteric propagation across a β -sheet structure investigated by molecular dynamics simulations

Gianluca Interlandi [University of Washington, Seattle] and Wendy E. Thomas

Proteins: Stru. Fun. & Bioinf., **84**, 990–1008, 2016.

The bacterial adhesin FimH consists of an allosterically regulated mannose-binding lectin domain and a covalently linked inhibitory pilin domain. Under normal conditions, the two domains are bound to each other, and FimH interacts weakly with mannose. Molecular dynamics simulations investigated how conformational changes are propagated within and between different regions of the lectin domain. It was found that the inter-domain region moves towards the high affinity conformation as it becomes more compact and buries exposed hydrophobic surface after separation of the pilin domain.

Protein Structure Prediction

FRAGSION: ultra-fast protein fragment library generation by IOHMM sampling

Debswapna Bhattacharya, Badri Adhikari, Jilong Li, and Jianlin Cheng [University of Missouri, Columbia]

Bioinformatics. **32**, 2059-2061, 2016.

Speed, accuracy and robustness of building protein fragment library have important implications in de novo protein structure prediction since fragment-based methods are one of the most successful approaches in template-free modeling (FM). Majority of the existing fragment detection methods rely on database-driven search strategies to identify candidate fragments, which are inherently time-consuming and often hinder the possibility to locate longer fragments due to the limited sizes of databases. Here, we present FRAGSION, a database-free method to efficiently generate protein fragment library by sampling from an Input–Output Hidden Markov Model.

Comparative or Homology Modeling

ASDB: a resource for probing protein functions with small molecules

Zhihong Liu, Peng Ding, Xin Yan, Minghao Zheng, Huihao Zhou, Yuehua Xu, Yunfei Du, Qiong Gu, and Jun Xu [Sun Yat-sen University]

Bioinformatics. **32**, 1752-1754, 2016.

Identifying chemical probes or seeking scaffolds for a specific biological target is important for protein function studies. Therefore, we create the Annotated Scaffold Database (ASDB), a computer-readable and systematic target-annotated scaffold database, to serve such needs. The scaffolds in ASDB were derived from public databases including ChEMBL, DrugBank and TCMSP, with a scaffold-based classification approach. Each scaffold was assigned with an InChIKey as its unique identifier, energy-minimized 3D conformations, and other calculated properties.

Protein Conformational Analysis

Conformational and Thermodynamic Landscape of GPCR Activation from Theory and Computation

Sijia S. Dong, William A. Goddard III, Ravinder Abrol [California Institute of Technology, Pasadena]

Biophysical Journal., **110**, 2618-2629, 2016.

We present a hybrid computational methodology to predict multiple energetically accessible conformations for G protein-coupled receptors (GPCRs) that might play a role in binding to ligands and different signaling partners. To our knowledge, this method, termed ActiveGenSeMBLE, enables the first quantitative energy profile for GPCR activation that is consistent with the qualitative profile deduced from experiments. ActiveGenSeMBLE starts with a systematic coarse grid sampling of helix tilts/rotations (~13 trillion transmembrane-domain conformations) and selects the conformational landscape based on energy.

Traversing the folding pathway of proteins using temperature-aided cascade molecular dynamics with conformation-dependent charges

Vinod Jani, Uddhavesh Sonavane, Rajendra Joshi [Centre for Development of Advanced Computing (C-DAC), Pune]

Euro. Biophysical Journal., **45**, 463-482, 2016.

Protein folding is a multi-micro second time scale event and involves many conformational transitions. Crucial conformational transitions responsible for biological functions of biomolecules are difficult to capture using current state-of-the-art molecular dynamics (MD) simulations. Protein folding, being a stochastic process, witnesses these transitions as rare events. Many new methodologies have been proposed for observing these rare events. In this work, a temperature-aided cascade MD is proposed as a technique for studying the conformational transitions.

Computational Insights into the Stability and Folding Pathways of Human Telomeric DNA G-Quadruplexes

Di Luo and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B., **120**, 4912-4926, 2016.

G-quadruplex is a noncanonical yet crucial secondary structure of nucleic acids, which has proven its importance in cell aging, anticancer therapies, gene expression, and genome stability. In this study, the stability and folding dynamics of human telomeric DNA G-quadruplexes were investigated via enhanced sampling techniques. First, temperature-replica exchange MD (REMD) simulations were employed to compare the thermal stabilities among the five established folding topologies. The hybrid-2 type adopted by extended human telomeric sequence is revealed to be the most stable conformation in our simulations.

Protein Structure Analysis

Ensemble-based evaluation for protein structure models

Michal Jamroz, Andrzej Kolinski, and Daisuke Kihara
[Purdue University, West Lafayette]

Bioinformatics. **32**, i314-i321, 2016.

Comparing protein tertiary structures is a fundamental procedure in structural biology and protein bioinformatics. Structure comparison is important particularly for evaluating computational protein structure models. We propose a score named FlexScore for comparing protein structures that consider flexibility of each residue in the native state of proteins. Flexibility information may be extracted from experiments such as NMR or molecular dynamics simulation. FlexScore considers an ensemble of conformations of a protein described as a multivariate Gaussian distribution of atomic displacements and compares a query computational model with the ensemble.

Computational approaches for predicting mutant protein stability

Shweta Kulshreshtha [Amity University Rajasthan], Vigi Chaudhary, Girish K. Goswami, Nidhi Mathur

J.Comp.Aided. Mol.des. **30**, 401-412, 2016.

Mutations in the protein affect not only the structure of protein, but also its function and stability. Prediction of mutant protein stability with accuracy is desired for uncovering the molecular aspects of diseases and design of novel proteins. Many advanced computational approaches have been developed over the years, to predict the stability and function of a mutated protein. These approaches based on structure, sequence features and combined features (both structure and sequence features) provide reasonably accurate estimation of the impact of amino acid substitution on stability and function of protein.

Stability of a Recently Found Triple- β -Stranded A β 1–42 Fibril Motif

Wenhui Xi, Wenhua Wang, Gabrielle Abbott, and Ulrich H. E. Hansmann [University of Oklahoma, Norman]

J. Phys. Chem. B., **120**, 4548–4557, 2016.

Amyloid- β peptides form polymorphous amyloid fibrils are correlated with the pathogenesis of Alzheimer's disease. Recently, a new ssNMR high-resolution structure has been reported for wild-type A β 1–42 fibrils that is characterized by a strand-turn-strand-turn-strand motif instead of the U-shape form seen in previously known wild-type A β -fibril structures. Analyzing molecular dynamics simulations we comment on the relative weight of the new fibril structure and present evidence that its stability depends on hydrophobic contacts involving the C-terminal residues I41 and A42, but not on the salt bridge K28–A42.

Structure of Penta-Alanine Investigated by Two-Dimensional Infrared Spectroscopy and Molecular Dynamics Simulation

Yuan Feng, Jing Huang, Seongheun Kim, Ji Hyun Shim, Alexander D. MacKerell Jr., and Nien-Hui Ge [University of California at Irvine]

J. Phys. Chem. B., **120**, 5325–5339, 2016.

We have studied the structure of (Ala)₅, a model unfolded peptide, using a combination of 2D IR spectroscopy and MD simulation. Two different isotopomers, each bis-labeled with ¹³C=O and ¹³C=¹⁸O, were strategically designed to shift individual site frequencies and uncouple neighboring amide-I' modes. 2D IR spectra taken under the double-crossed ($\pi/4$, $-\pi/4$, Y, Z) polarization show that the labeled four-oscillator systems can be approximated by three two-oscillator systems.

Protein Engineering

Library of binding protein scaffolds (LibBP): a computational platform for selection of binding protein scaffolds

Seungpyo Hong and Dongsup Kim [Department of Bio and Brain Engineering, KAIST]

Bioinformatics. **32**, 1709-1715, 2016.

Developments in biotechnology have enabled the *in vitro* evolution of binding proteins. The emerging limitations of antibodies in binding protein engineering have led to suggestions for other proteins as alternative binding protein scaffolds. For each protein, its structure and the sequences of evolutionarily-related proteins were analyzed, and spatially contiguous regions composed of highly variable residues were identified. A large number of proteins have these regions, but leucine rich repeats (LRRs), histidine kinase domains and immunoglobulin domains are predominant among them.

Protein Dynamics

Thermal stability and unfolding pathways of hyperthermophilic and mesophilic periplasmic binding proteins studied by molecular dynamics simulation

Lin Chen, Xue Li, Ruige Wang, Fengqin Fang, Wanli Yang & Wei Kan [Qiqihar University]

J. Biomol. Stru. and Dyn., **34**, 1576-1589, 2016.

The ribose binding protein (RBP), a sugar-binding periplasmic protein, is involved in the transport and signaling processes in both prokaryotes and eukaryotes. Although several cellular and structural studies have been reported, a description of the thermostability of RBP at the molecular level remains elusive. Focused on the hyperthermophilic *Thermotoga maritima* RBP (tmRBP) and mesophilic *Escherichia coli* homolog (ecRBP), we applied molecular dynamics simulations at four different temperatures (300, 380, 450, and 500 K) to obtain a deeper insight into the structural features responsible for the reduced thermostability of the ecRBP.

Protein environmental effects on iron-sulfur clusters: A set of rules for constructing computational models for inner and outer coordination spheres

Travis V. Harris and Robert K. Szilagyi [Montana State University, Bozeman]

J. Comp. Chem., **37**, 1681–1696, 2016.

The structural properties and reactivity of iron-sulfur proteins are greatly affected by interactions between the prosthetic groups and the surrounding amino acid residues. Thus, quantum chemical investigations of the structure and properties of protein-bound iron-sulfur clusters can be severely limited by truncation of computational models. The aim of this study was to identify, *a priori*, significant interactions that must be included in a quantum chemical model.

pH effects on adsorption behavior and self-aggregation of dodecylamine at muscovite/aqueous interfaces

Li Wang, Runqing Liu, Yuehua Hu, Wei Sun [Central South University Changsha]

J. Mol.Graph. and Mod., **66**, 62-68, 2016.

In this work, molecular dynamics simulation was used to examine the effect of solution pH on the adsorption behavior and self-aggregation of dodecylamine hydrochloride (DDA) on the muscovite (0 0 1) surface. The properties of surfactants are assessed in terms of density profiles in the direction perpendicular to the muscovite surface. Results show that although DDA can adsorb at muscovite at all pH we discussed, the self-aggregation of DDA varies significantly at different pH values. At pH 10, a compact hydrophobic monolayer forms on the muscovite surface.

Protein Dynamics (Cont'd)

Mechanisms of histone lysine-modifying enzymes: A computational perspective on the role of the protein environment

Wiliam Augusto Cortopassi, Kiran Kumar, Fernanda Duarte, Andre Silva Pimentel, Robert S. Paton [Chemistry Research Laboratory, 12 Mansfield Road, Oxford]

J. Mol.Graph. and Mod., **66**, 69-84, 2016.

Epigenetic pathways are involved in a wide range of diseases, including cancer and neurological disorders. Specifically, histone modifying and reading processes are the most broadly studied and are targeted by several licensed drugs. Experimentally, it is generally difficult to elucidate the atomistic basis for substrate recognition, as well as the sequence of events involved in binding and the subsequent chemical processes. In this regard, computational modelling is particularly valuable, since it can provide structural features (including transition state structures along with kinetic and thermodynamic parameters) that enable both qualitative and quantitative evaluation of the mechanistic details involved.

Thermostability of Enzymes from Molecular Dynamics Simulations

Tim Zeiske, Kate A. Stafford, and Arthur G. Palmer III [Columbia University, New York]

J. Chem. Theor. and Comp., **12**, 2489–2492, 2016.

Thermodynamic stability is a central requirement for protein function, and one goal of protein engineering is improvement of stability, particularly for applications in biotechnology. Herein, molecular dynamics simulations are used to predict in vitro thermostability of members of the bacterial ribonuclease HI (RNase H) family of endonucleases. The temperature dependence of the generalized order parameter, S , for four RNase H homologues, from psychrotrophic, mesophilic, and thermophilic organisms, is highly correlated with experimentally determined melting temperatures and with calculated free energies of folding at the midpoint temperature of the simulations.

Computational study of pH-dependent oligomerization and ligand binding in Alt a 1, a highly allergenic protein with a unique fold

María Garrido-Arandia, Jorge Bretones, Cristina Gómez-Casado, Nuria Cubells, Araceli Díaz-Perales, Luis F. Pacios [Technical University of Madrid]

J.Comp.Aided. Mol.des. **30**, 365-379, 2016.

Alt a 1 is a highly allergenic protein from *Alternaria* fungi responsible for several respiratory diseases. Its crystal structure revealed a unique β -barrel fold that defines a new family exclusive to fungi and forms a symmetrical dimer in a butterfly-like shape as well as tetramers. . By means of a combined computational study that includes docking calculations, empirical pKa estimates, Poisson–Boltzmann electrostatic potentials, and Molecular Dynamics simulations, we identified a putative binding site at the dimeric interface between subunits in tetramer.

Free Energy Calculations

Rapid approximate calculation of water binding free energies in the whole hydration domain of (bio)macromolecules

Maria M. Reif and Martin Zacharias [Technische Universität München]

J. Comp. Chem., **37**, 1711–1724, 2016.

The evaluation of water binding free energies around solute molecules is important for the thermodynamic characterization of hydration or association processes. Here, a rapid approximate method to estimate water binding free energies around (bio)macromolecules from a single molecular dynamics simulation is presented. The basic idea is that endpoint free-energy calculation methods are applied and the endpoint quantities are monitored on a three-dimensional grid around the solute.

Ligand Binding/Docking

Investigation on critical structural motifs of ligands for triggering glucocorticoid receptor nuclear migration through molecular docking simulations

Ya-Lin Liu, Soonmin Jang, Shih-Min Wang, Chiu-Hao Chen & Feng-Yin Li [National Chung Hsing University]

J. Biomol. Stru. and Dyn., **34**, 1214-1231, 2016.

The glucocorticoid receptor (GR), a transcription factor regulating gene expression in a ligand-dependent fashion, is known for flexibility in adapting various ligands with their structures ranging from steroid to non-steroid. However, in our previous study, GR shows a stringent discrimination against a set of steroid ligands with highly similar structures for triggering its nuclear migration. In order to resolve this puzzle, we employed molecular docking simulations to investigate the origin of this structural discrimination.

Structural investigations into the binding mode of novel neolignans Cmp10 and Cmp19 microtubule stabilizers by in silico molecular docking, molecular dynamics, and binding free energy calculations

Shubhendra Tripathi, Akhil Kumar, B. Sathish Kumar, Arvind S. Negi & Ashok Sharma [CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP)]

J. Biomol. Stru. and Dyn., **34**, 1232-1240, 2016.

Microtubule stabilizers provide an important mode of treatment via mitotic cell arrest of cancer cells. Recently, we reported two novel neolignans derivatives Cmp10 and Cmp19 showing anticancer activity and working as microtubule stabilizers at micromolar concentrations. In this study, we have explored the binding site, mode of binding, and stabilization by two novel microtubule stabilizers Cmp10 and Cmp19 using in silico molecular docking, molecular dynamics (MD) simulation, and binding free energy calculations. Molecular docking studies were performed to explore the β -tubulin binding site of Cmp10 and Cmp19.

Molecular insight into amyloid oligomer destabilizing mechanism of flavonoid derivative 2-(4' benzyloxyphenyl)-3-hydroxy-chromen-4-one through docking and molecular dynamics simulations

Akhil Kumar, Swati Srivastava, Shubhendra Tripathi, Sandeep Kumar Singh, Saripella Srikrishna & Ashok Sharma [CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP)]

J. Biomol. Stru. and Dyn., **34**, 1252-1263, 2016.

Aggregation of amyloid peptide (A β) has been shown to be directly related to progression of Alzheimer's disease (AD). A β is neurotoxic and its deposition and aggregation ultimately lead to cell death. In our previous work, we reported flavonoid derivative showing promising result in transgenic AD model of *Drosophila*. Compound 1 showed prevention of A β -induced neurotoxicity and neuroprotective efficacy in *Drosophila* system. However, mechanism of action of compound 1 and its effect on the amyloid is not known. We therefore performed molecular docking and atomistic, explicit-solvent MD simulations to investigate the process of A β interaction, inhibition, and destabilizing mechanism.

Ligand Binding / Docking (Cont'd)

Cations Stiffen Actin Filaments by Adhering a Key Structural Element to Adjacent Subunits

Cruz, and Gregory A. Voth [The University of Chicago, Chicago]

J. Phys. Chem. B., **120**, 4558–4567, 2016.

Ions regulate the assembly and mechanical properties of actin filaments. Recent work using structural bioinformatics and site-specific mutagenesis favors the existence of two discrete and specific divalent cation binding sites on actin filaments, positioned in the long axis between actin subunits. Cation binding at one site drives polymerization, while the other modulates filament stiffness and plays a role in filament severing by the regulatory protein, cofilin. In this work we turn to molecular dynamics simulations to suggest a candidate binding pocket geometry for each site and to elucidate the mechanism by which occupancy of the “stiffness site” affects filament mechanical properties.

Enzyme Catalysis

A molecular dynamics study of Beta-Glucosidase B upon small substrate binding

Nur Shima Fadhilah Mazlan & Nurul Bahiyah Ahmad Khairudin [Universiti Teknologi Malaysia Kuala Lumpur]

J. Biomol. Stru. and Dyn., **34**, 1486-1494, 2016.

Paenibacillus polymyxa β -glucosidase B (BglB), belongs to a GH family 1, is a monomeric enzyme that acts as an exo- β -glucosidase hydrolysing cellobiose and celloextrins of higher degree of polymerization using retaining mechanism. A MD simulation was performed at 300 K under periodic boundary condition for 5 ns using the complexes structure obtained from previous docking study, namely BglB-Beta-d-glucose and BglB-Cellobiose. From the root-mean-square deviation analysis, both enzyme complexes were reported to deviate from the initial structure in the early part of the simulation but it was stable afterwards.

Structural and dynamical correlations in PfHGXPR T oligomers: A molecular dynamics simulation study

Tarak Karmakar, Sourav Roy, Hemalatha Balaram & Sundaram Balasubramanian [Jawaharlal Nehru Centre for Advanced Scientific Research]

J. Biomol. Stru. and Dyn., **34**, 1590-1605, 2016.

PfHGXPR T is a key enzyme involved in purine nucleotide salvage pathway of the malarial parasite, *Plasmodium falciparum*. Atomistic molecular dynamics simulations have been performed on two types of PfHGXPR T dimers (D1 and D3) and its tetramer in their apo and ligand-bound states. A significant event in the catalytic cycle is the dynamics of a gate that provides access for the ligand molecules to the reaction center.

Improved free energy profile for reduction of NO in cytochrome c dependent nitric oxide reductase (cNOR)

Margareta R. A. Blomberg [Stockholm University] and Per E. M. Siegbahn

J. Comp. Chem., **37**, 1810–1818, 2016.

Quantum chemical calculations play an essential role in the elucidation of reaction mechanisms for redox-active metalloenzymes. For example, the cleavage and the formation of covalent bonds can usually not be described only on the basis of experimental information, but can be followed by the calculations. Conversely, there are properties, like reduction potentials, which cannot be accurately calculated. Therefore, computational and experimental data has to be carefully combined to obtain reliable descriptions of entire catalytic cycles involving electron and proton uptake from donors outside the enzyme.

Enzyme Catalysis (Cont'd)

Computational docking, molecular dynamics simulation and subsite structure analysis of a maltogenic amylase from *Bacillus lehensis* G1 provide insights into substrate and product specificity

Nor Hasmaliana Abdul Manas, Farah Diba Abu Bakar, Rosli Md. Illias [Universiti Teknologi Malaysia]

J. Mol.Graph. and Mod., **66**, 1-13, 2016.

Maltogenic amylase (MAG1) from *Bacillus lehensis* G1 displayed the highest hydrolysis activity on β -cyclodextrin (β -CD) to produce maltose as a main product and exhibited high transglycosylation activity on malto-oligosaccharides with polymerization degree of three and above. These substrate and product specificities of MAG1 were elucidated from structural point of view in this study. A three-dimensional structure of MAG1 was constructed using homology modeling. Docking of β -CD and malto-oligosaccharides was then performed in the MAG1 active site.

Discerning the catalytic mechanism of *Staphylococcus aureus* sortase A with QM/MM free energy calculations

Pooja Shrestha, Jeff Wereszczynski [Illinois Institute of Technology]

J. Mol.Graph. and Mod., **66**, 33-43, 2016.

Sortases are key virulence factors in Gram-positive bacteria. These enzymes embed surface proteins in the cell wall through a transpeptidation reaction that involves recognizing a penta-peptide "sorting signal" in a target protein, cleaving it, and covalently attaching it to a second substrate that is later inserted into the cell wall. To determine which of these is the biologically relevant state, we have performed a series of conventional and hybrid quantum mechanics/molecular mechanics (QM/MM) molecular dynamics simulations of the *Staphylococcus aureus* sortase A (SrtA) enzyme bound to a sorting signal substrate.

Molecular Dynamics Simulations Elucidate Conformational Dynamics Responsible for the Cyclization Reaction in TEAS

Fan Zhang, Nanhao Chen, and Ruibo Wu [Sun Yat-sen University]

J.Chem. Infor. and Mod., **56**, 877–885, 2016.

The Mg-dependent 5-epi-aristolochene synthase from *Nicotiana tabacum* (called TEAS) could catalyze the linear farnesyl pyrophosphate (FPP) substrate to form bicyclic hydrocarbon 5-epi-aristolochene. The cyclization reaction mechanism of TEAS was proposed based on static crystal structures and quantum chemistry calculations in a few previous studies, but substrate FPP binding kinetics and protein conformational dynamics responsible for the enzymatic catalysis are still unclear. Herein, by elaborative and extensive molecular dynamics simulations, the loop conformation change and several crucial residues promoting the cyclization reaction in TEAS are elucidated.

Predictive Models for Fast and Effective Profiling of Kinase Inhibitors

Alina Bora, Sorin Avram [Timisoara of Romanian Academy], Ionel Ciucanu, Marius Raica, and Stefana Avram

J.Chem. Infor. and Mod., **56**, 895–905, 2016.

In this study we developed two-dimensional pharmacophore-based random forest models for the effective profiling of kinase inhibitors. One hundred seven prediction models were developed to address distinct kinases spanning over all kinase groups. Rigorous external validation demonstrates excellent virtual screening and classification potential of the predictors and, more importantly, the capacity to prioritize novel chemical scaffolds in large chemical libraries.

Enzyme Catalysis (Cont'd)

Insights into the Reaction Mechanism of Aromatic Ring Cleavage by Homogentisate Dioxygenase: A Quantum Mechanical/Molecular Mechanical Study

Yue Qi, Jiarui Lu, and Wenzhen Lai [Renmin University of China]

J. Phys. Chem. B., **120**, 4579–4590, 2016.

To elucidate the reaction mechanism of the ring cleavage of homogentisate by homogentisate dioxygenase, quantum mechanical/molecular mechanical (QM/MM) calculations were carried out by using two systems in different protonation states of the substrate C₂ hydroxyl group. When the substrate C₂ hydroxyl group is ionized (the ionized pathway), the superoxo attack on the substrate is the rate-limiting step in the catalytic cycle, with a barrier of 15.9 kcal/mol. Glu396 was found to play an important role in stabilizing the bridge species and its O–O cleavage product by donating a proton via a hydrogen-bonded water molecule.

Enzyme Catalysis that Paves the Way for S-Sulphydration via Sulfur Atom Transfer

Gou-Tao Huang and Jen-Shiang K. Yu [National Chiao Tung University]

J. Phys. Chem. B., **120**, 4608–4615, 2016.

S-sulphydration is generally anticipated to proceed through the transfer of the SH group ($\text{Nu-SH} \cdots \text{S-R} \rightarrow \text{Nu} \cdots \text{HS-S-R}$). The other route involves the sulfur atom (S^0) transfer between two sulfhydryl anions ($\text{Nu-S}^- \cdots \text{S-R} \rightarrow \text{Nu} \cdots \text{S-S-R}$) and is considered electrostatically unfavorable. Mercaptopyruvate sulfurtransferase (MST, PDB code: [4JGT](#)) catalyzes sulfur transfer from mercaptopyruvate to sulfur acceptors, and the first step of the reaction is the formation of cysteine (Cys248) persulfide via S-sulphydration. Mechanistic studies on S-sulphydration in MST using QM/MM methods show that the sulfur atom transfer initialized by the deprotonation of the Ser250/His74/Asp63 triad is kinetically preferred to the SH-promoted sulfur transfer.

Molecular dynamics simulations of apo, holo, and inactivator bound GABA-at reveal the role of active site residues in PLP dependent enzymes

Hatice Gökcan, Gerald Monard and F. Aylin Sungur Konuklar [Informatics Institute, Maslak]

Proteins: Stru. Fun. & Bioinf., **84**, 875–891, 2016.

The pyridoxal 5-phosphate (PLP) cofactor is a significant organic molecule in medicinal chemistry. It is often found covalently bound to lysine residues in proteins to form PLP dependent enzymes. An example of this family of PLP dependent enzymes is γ -aminobutyric acid aminotransferase (GABA-AT) which is responsible for the degradation of the neurotransmitter GABA. Its inhibition or inactivation can be used to prevent the reduction of GABA concentration in brain which is the source of several neurological disorders. As a test case for PLP dependent enzymes, we have performed molecular dynamics simulations of GABA-AT to reveal the roles of the protein residues and its cofactor.

Enzyme Catalysis (Cont'd)

Conservation of structural fluctuations in homologous protein kinases and its implications on functional sites

Raju Kalaivani, Alexandre G. de Brevern and Narayanaswamy Srinivasan [Indian Institute of Science, Bangalore]

Proteins: Stru. Fun. & Bioinf., **84**, 957–978, 2016.

Our aim is to explore the similarities in structural fluctuations of homologous kinases. Gaussian Network Model based Normal Mode Analysis was performed on 73 active conformation structures in Ser/Thr/Tyr kinase superfamily. Categories of kinases with progressive evolutionary divergence, viz. (i) Same kinase with many crystal structures, (ii) Within-Subfamily, (iii) Within-Family, (iv) Within-Group, and (v) Across-Group, were analyzed. We identified a flexibility signature conserved in all kinases involving residues in and around the catalytic loop with consistent low-magnitude fluctuations.

Protein-Protein Interactions

Inclusion of dyad-repeat pattern improves topology prediction of transmembrane β -barrel proteins

Sikander Hayat, Christoph Peters, Nanjiang Shu, Konstantinos D. Tsirigos, and Arne Elofsson [Swedish E-Science Research Center]

Bioinformatics. **32**, 1571-1573, 2016.

Accurate topology prediction of transmembrane β -barrels is still an open question. Here, we present BOCTOPUS2, an improved topology prediction method for transmembrane β -barrels that can also identify the barrel domain, predict the topology and identify the orientation of residues in transmembrane β -strands. The major novelty of BOCTOPUS2 is the use of the dyad-repeat pattern of lipid and pore facing residues observed in transmembrane β -barrels.

Finding correct protein–protein docking models using ProQDock

Sankar Basu and Björn Wallner [Linköping University]

Bioinformatics. **32**, i262-i270, 2016.

Protein–protein interactions are a key in virtually all biological processes. For a detailed understanding of the biological processes, the structure of the protein complex is essential. Given the current experimental techniques for structure determination, the vast majority of all protein complexes will never be solved by experimental techniques. Here, we present ProQDock, a scoring function that predicts the absolute quality of docking model measured by a novel protein docking quality score (DockQ). ProQDock uses support vector machines trained to predict the quality of protein docking models using features that can be calculated from the docking model itself.

Predicting physiologically relevant SH3 domain mediated protein–protein interactions in yeast

Shobhit Jain and Gary D. Bader [University of Toronto]

Bioinformatics. **32**, 1865-1872, 2016.

Many intracellular signaling processes are mediated by interactions involving peptide recognition modules such as SH3 domains. These domains bind to small, linear protein sequence motifs which can be identified using high-throughput experimental screens such as phage display. A novel method for predicting physiologically relevant SH3 domain-peptide mediated protein–protein interactions in *S. cerevisiae* using phage display data is presented.

Protein - Protein Interactions (Cont'd)

Ranking protein–protein docking results using steered molecular dynamics and potential of mean force calculations

Laura J. Kingsley, Juan Esquivel-Rodríguez, Ying Yang, Daisuke Kihara and Markus A. Lill [Purdue University, West Lafayette]

J. Comp. Chem., **37**, 1861–1865, 2016.

Crystallization of protein–protein complexes can often be problematic and therefore computational structural models are often relied on. Such models are often generated using protein–protein docking algorithms, where one of the main challenges is selecting which of several thousand potential predictions represents the most near-native complex. We have developed a novel technique that involves the use of steered molecular dynamics (sMD) and umbrella sampling to identify near-native complexes among protein–protein docking predictions.

New Computational Approach for External Entropy in Protein–Protein Binding

Song-Ho Chong and Sihyun Ham [Sookmyung Women's University]

J. Chem. Theor. and Comp, **12**, 2509–2516, 2016.

Molecular recognition through the noncovalent association of biomolecules is of central importance in biology and pharmacology. Here, we present a novel statistical mechanical method for computing the external entropy by extending the energetic approach we have developed for unimolecular processes to association processes. We find that, in contrary to what is postulated in most of the previous methods, intrinsic couplings between the internal and external degrees of freedom of bound complex cannot in general be neglected in the determination of the external entropy.

Interplay between binding affinity and kinetics in protein–protein interactions

Huaiqing Cao, Yongqi Huang and Zhirong Liu [Peking University, Beijing]

Proteins: Stru. Fun. & Bioinf., **84**, 920–933, 2016.

To clarify the interplay between the binding affinity and kinetics of protein–protein interactions, and the possible role of intrinsically disordered proteins in such interactions, molecular simulations were carried out on 20 protein complexes. With bias potential and reweighting techniques, the free energy profiles were obtained under physiological affinities, which showed that the bound-state valley is deep with a barrier height of 12–33 RT. From the dependence of the affinity on interface interactions, the entropic contribution to the binding affinity is approximated to be proportional to the interface area.

Membrane Proteins and Lipid Peptide Interactions

Alloscore: a method for predicting allosteric ligand–protein interactions

Shuai Li, Qiancheng Shen, Minyi Su, Xinyi Liu, Shaoyong Lu, Zhongjie Chen, Renxiao Wang, and Jian Zhang [Shanghai Jiao-Tong University School of Medicine]

Bioinformatics. **32**, 1574-1576, 2016.

Allosteric ligands have increasingly gained attention as potential therapeutic agents due to their higher target selectivity and lower toxicity compared with classic orthosteric ligands. Despite the great interest in the development of allosteric drugs as a new tactic in drug discovery, the understanding of the ligand–protein interactions underlying allosteric binding represents a key challenge. Herein, we introduce Alloscore, a web server that predicts the binding affinities of allosteric ligand–protein interactions.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Sodium chloride's effect on self-assembly of diphenylalanine bilayer

Junpyo Kwon, Myeongsang Lee and Sungsoo Na [Korea University, Seoul]

J. Comp. Chem., **37**, 1839–1846, 2016.

Understanding self-assembling peptides becomes essential in nanotechnology, thereby providing a bottom-up method for fabrication of nanostructures. Diphenylalanine constitutes an outstanding building block that can be assembled into various nanostructures, including two-dimensional bilayers or nanotubes, exhibiting superb mechanical properties. In this study, we analyzed the effect of sodium chloride on diphenylalanine bilayer using coarse-grained molecular dynamics simulations, and calculated the bending Young's modulus and the torsional modulus by applying normal modal analysis using an elastic network model.

PBSA_E: A PBSA-Based Free Energy Estimator for Protein–Ligand Binding Affinity

Xiao Liu, Jinfeng Liu, Tong Zhu, Lujia Zhang, Xiao He, and John Z. H. Zhang [East China Normal University]

J. Chem. Infor. and Mod., **56**, 854–861, 2016.

Improving the accuracy of scoring functions for estimating protein–ligand binding affinity is of significant interest as well as practical utility in drug discovery. In this work, PBSA_E, a new free energy estimator based on the molecular mechanics/Poisson–Boltzmann surface area (MM/PBSA) descriptors, has been developed. This free energy estimator was optimized using high-quality experimental data from a training set consisting of 145 protein–ligand complexes. The method was validated on two separate test sets containing 121 and 130 complexes.

Quantifying the Heterogeneous Dynamics of a Simulated Dipalmitoylphosphatidylcholine (DPPC) Membrane

Neha Shafique, Kiley E. Kennedy, Jack F. Douglas, and Francis W. Starr [Wesleyan University, Middletown]

J. Phys. Chem. B., **120**, 5172–5182, 2016.

Heterogeneity of dynamics plays a vital role in membrane function, but the methods for quantifying this heterogeneity are still being developed. Here we examine membrane dynamical heterogeneity via molecular simulations of a single-component dipalmitoylphosphatidylcholine (DPPC) lipid bilayer using the MARTINI force field. We draw upon well-established analysis methods developed in the study of glass-forming fluids and find significant changes in lipid dynamics between the fluid (L_α), and gel (L_β) phases.

Elucidation of Nonadditive Effects in Protein–Ligand Binding Energies: Thrombin as a Case Study

Gaetano Calabrò, Christopher J. Woods, Francis Powlesland, Antonia S. J. S. Mey [University of Edinburgh], Adrian J. Mulholland, and Julien Michel

J. Phys. Chem. B., **120**, 5340–5350, 2016.

Accurate predictions of free energies of binding of ligands to proteins are challenging partly because of the nonadditivity of protein–ligand interactions; i.e., the free energy of binding is the sum of numerous enthalpic and entropic contributions that cannot be separated into functional group contributions. An efficient GPU-accelerated implementation of alchemical free energy calculations has been developed and applied to two congeneric series of ligands of the enzyme thrombin.

Protein Design

Protein backbone ensemble generation explores the local structural space of unseen natural homologs

Christian D. Schenkelberg and Christopher Bystroff
[Rensselaer Polytechnic Institute]

Bioinformatics, **32**, 1454-1461, 2016.

Mutations in homologous proteins affect changes in the backbone conformation that involve a complex interplay of forces which are difficult to predict. Protein design algorithms need to anticipate these backbone changes in order to accurately calculate the energy of the structure given an amino acid sequence, without knowledge of the final, designed sequence. We explored the ability of the Rosetta suite of protein design tools to move the backbone from its position in one structure (template) to its position in a close homologous structure (target) as a function of the diversity of a backbone ensemble constructed using the template structure, the percent sequence identity between the template and target, and the size of local zone being considered in the ensemble.

Comparing three stochastic search algorithms for computational protein design: Monte Carlo, replica exchange Monte Carlo, and a multistart, steepest-descent heuristic

David Mignon and Thomas Simonson [Ecole Polytechnique, Palaiseau]

J. Comp. Chem., **37**, 1781–1793, 2016.

Computational protein design depends on an energy function and an algorithm to search the sequence/conformation space. We compare three stochastic search algorithms: a heuristic, Monte Carlo (MC), and a Replica Exchange Monte Carlo method (REMC). The heuristic performs a steepest-descent minimization starting from thousands of random starting points. The methods are applied to nine test proteins from three structural families, with a fixed backbone structure, a molecular mechanics energy function, and with 1, 5, 10, 20, 30, or all amino acids allowed to mutate.

Protein Folding

Necessity of high-resolution for coarse-grained modeling of flexible proteins

Zhiguang Jia and Jianhan Chen [Kansas State University, Manhattan]

J. Comp. Chem., **37**, 1725–1733, 2016.

The popular MARTINI coarse-grained (CG) force field requires the protein structure to be fixed, and is unsuitable for simulating dynamic processes such as protein folding. Here, we examine the feasibility of developing a flexible protein model within the MARTINI framework. The results demonstrate that the MARTINI CG scheme does not properly describe the volume and packing of protein backbone and side chains and leads to excessive collapse without structural restraints in explicit CG water.

Protein Folding (Cont'd)

Radical Formation Initiates Solvent-Dependent Unfolding and β -sheet Formation in a Model Helical Peptide

Michael C. Owen [Institute of Complex Systems: Structural Biochemistry (ICS-6), Forschungszentrum Jülich], Birgit Strodel, Imre G. Csizmadia, and Béla Viskolcz

J. Phys. Chem. B., **120**, 4878–4889, 2016.

We examined the effects of C_{α} -centered radical formation on the stability of a model helical peptide, N-Ac-KK(AL)₁₀KK-NH₂. Three, 100 ns molecular dynamics simulations using the OPLS-AA force field were carried out on each α -helical peptide in six distinct binary TIP4P water/2,2,2-trifluoroethanol (TFE) mixtures. The α -helicity was at a maximum in 20% TFE, which was inversely proportional to the number of H-bonds between water molecules and the peptide backbone. The radial distribution of TFE around the peptide backbone was highest in 20% TFE, which enhanced helix stability.

Protein-Nucleic acid Interactions

Convolutional neural network architectures for predicting DNA–protein binding

Haoyang Zeng, Matthew D. Edwards, Ge Liu, and David K. Gifford [Massachusetts Institute of Technology]

Bioinformatics. **32**, i121–i127, 2016.

Convolutional neural networks (CNN) have outperformed conventional methods in modeling the sequence specificity of DNA–protein binding. Yet inappropriate CNN architectures can yield poorer performance than simpler models. We present a systematic exploration of CNN architectures for predicting DNA sequence binding using a large compendium of transcription factor datasets. We identify the best-performing architectures by varying CNN width, depth and pooling designs. We find that adding convolutional kernels to a network is important for motif-based tasks.

RCK: accurate and efficient inference of sequence- and structure-based protein–RNA binding models from RNAcompete data

Yaron Orenstein, Yuhao Wang, and Bonnie Berger [Math Department, MIT]

Bioinformatics. **32**, i351–i359, 2016.

Protein–RNA interactions, which play vital roles in many processes, are mediated through both RNA sequence and structure. CLIP-based methods, which measure protein–RNA binding in vivo, suffer from experimental noise and systematic biases, whereas in vitro experiments capture a clearer signal of protein RNA-binding. We develop RCK, an efficient, scalable algorithm that infers both sequence and structure preferences based on a new k-mer based model. Remarkably, even though RNAcompete data is designed to be unstructured, RCK can still learn structural preferences from it.

Measuring the spatial correlations of protein binding sites

Yingying Wei and Hao Wu [Emory University, Atlanta]

Bioinformatics. **32**, 1766–1772, 2016.

Understanding the interactions of different DNA binding proteins is a crucial first step toward deciphering gene regulatory mechanism. With advances of high-throughput sequencing technology such as ChIP-seq, the genome-wide binding sites of many proteins have been profiled under different biological contexts. We discover a Simpson's paradox phenomenon in assessing the genome-wide spatial correlation of protein binding sites. Leveraging information from publicly available data, we propose a procedure for evaluating the significance of overlapping from a pair of proteins, which accounts for background artifacts and genome heterogeneity.

Nucleic Acids

Translation Initiation is Controlled by RNA Folding Kinetics via a Ribosome Drafting Mechanism

Amin Espah Borujeni and Howard M Salis [The Pennsylvania State University]

J. Am. Chem. Soc., **138**, 7016–7023, 2016.

RNA folding plays an important role in controlling protein synthesis as well as other cellular processes. Existing models have focused on how RNA folding energetics control translation initiation rate under equilibrium conditions but have largely ignored the effects of nonequilibrium RNA folding. We introduce a new mechanism, called “ribosome drafting”, that explains how a mRNA’s folding kinetics and the ribosome’s binding rate collectively control its translation initiation rate. During cycles of translation, ribosome drafting emerges whenever successive ribosomes bind to a mRNA faster than the mRNA can refold, maintaining it in a nonequilibrium state with an acceleration of protein synthesis.

Dynamical Disorder in the DNA Hydration Shell

Elise Duboué-Dijon, Aoife C. Fogarty, James T. Hynes, and Damien Laage [Département de Chimie, PASTEUR]

J. Am. Chem. Soc., **138**, 7610–7620, 2016.

The reorientation and hydrogen-bond dynamics of water molecules within the hydration shell of a B-DNA dodecamer, which are of interest for many of its biochemical functions, are investigated via molecular dynamics simulations and an analytic jump model, which provide valuable new molecular level insights into these dynamics. Different sources of heterogeneity in the hydration shell dynamics are determined. First, a pronounced spatial heterogeneity is found at the DNA interface and explained via the jump model by the diversity in local DNA interfacial topographies and DNA–water H-bond interactions.

Structural modeling and molecular simulation analysis of HvAP2/EREBP from barley

Bharati Pandey, Pradeep Sharma, Chetna Tyagi, Sukriti Goyal, Abhinav Grover & Indu Sharma [ICAR-Indian Institute of Wheat and Barley]

J. Biomol. Stru. and Dyn., **34**, 1159-1175, 2016.

AP2/ERF transcription factors play a critical role in plant development and stress adaptation. This study reports the three-dimensional ab initio-based model of AP2/EREBP protein of barley and its interaction with DNA. Full-length coding sequence of HvAP2/EREBP gene isolated from two Indian barley cultivars, RD 2503 and RD 31, was used to model the protein. Of five protein models obtained, the one with lowest C-score was chosen for further analysis. The N- and C-terminal regions of HvAP2 protein were found to be highly disordered.

Nucleic Acids (Cont'd)

Metal binding mediated conformational change of XPA protein: a potential cytotoxic mechanism of nickel in the nucleotide excision repair

Jianping Hu, Ziheng Hu, Yan Zhang, Xiaojun Gou, Ying Mu, Lirong Wang, Xiang-Qun Xie [University of Pittsburgh]

J. Mol. Mod., **22**, 156, 2016.

Nucleotide excision repair (NER) is a pivotal life process for repairing DNA nucleotide mismatch caused by chemicals, metal ions, radiation, and other factors. As the initiation step of NER, the xeroderma pigmentosum complementation group A protein (XPA) recognizes damaged DNA molecules, and recruits the replication protein A (RPA), another important player in the NER process. In this study, we first calculated the force field parameters for the bonded model in the metal center of the XPA₉₈₋₂₁₀ system, showing that the calculated results, including charges, bonds, angles etc., are congruent with previously reported results measured by spectrometry experiments and quantum chemistry computation.

Study of a DNA Duplex by Nuclear Magnetic Resonance and Molecular Dynamics Simulations. Validation of Pulsed Dipolar Electron Paramagnetic Resonance Distance Measurements Using Triarylmethyl-Based Spin Labels

Alexander A. Lomzov, Eugeni A. Sviridov, Andrey V. Shernuykov, Georgiy Yu. Shevelev, Dmitrii V. Pyshnyi, and Elena G. Bagryanskaya [Novosibirsk State University]

J. Phys. Chem. B., **120**, 5125–5133, 2016.

Pulse dipole–dipole electron paramagnetic resonance (EPR) spectroscopy (double electron–electron resonance [DEER] or pulse electron–electron double resonance [PELDOR] and double quantum coherence [DQC]) allows for measurement of distances in biomolecules and can be used at low temperatures in a frozen solution. In this paper, a combination of molecular dynamics (MD) and nuclear magnetic resonance (NMR) methods was used for verification of interspin distances measured by the X-band DQC method.

Surfaces, Catalysts, and Materials Subjects

Molecular Dynamics Simulations of Aldol Condensation Catalyzed by Alkylamine-Functionalized Crystalline Silica Surfaces

Ki Chul Kim, Eric G. Moschetta, Christopher W. Jones, and Seung Soon Jang [Georgia Institute of Technology]

J. Am. Chem. Soc., **138**, 7664–7672, 2016.

Molecular dynamics simulations are performed to investigate the cooperatively catalyzed aldol condensation between acetone and 4-nitrobenzaldehyde on alkylamine (or alkylamine)-grafted silica surfaces, focusing on the mechanism of the catalytic activation of the acetone and 4-nitrobenzaldehyde by the acidic surface silanols followed by the nucleophilic attack of the basic amine functional group toward the activated reactant.

Spectroscopy and computational studies on the interaction of octyl, dodecyl, and hexadecyl derivatives of anionic and cationic surfactants with adenosine deaminase

Davood Ajloo, Najmeh Mahmoodabadi, Maryam Ghadamgahi & Ali Akbar Saboury [University of Tehran]

J. Biomol. Stru. and Dyn., **34**, 1495-1511, 2016.

Effects of sodium (octyl, dodecyl, hexadecyl) sulfate and their cationic analogous on the structure of adenosine deaminase (ADA) were investigated by fluorescence and circular dichroism spectroscopy as well as molecular dynamics simulation and docking calculation. Root-mean-square derivations, radius of gyration, solvent accessible surface area, and radial distribution function were obtained. The results showed that anionic and cationic surfactants reduce protein stability.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Towards cheminformatics-based estimation of drug therapeutic index: Predicting the protective index of anticonvulsants using a new quantitative structure-index relationship approach

Shangying Chen, Peng Zhang, Xin Liu, Chu Qin, Lin Tao, Cheng Zhang, Sheng Yong Yang, Yu Zong Chen, Wai Keung Chui [National University of Singapore]

J. Mol.Graph. and Mod., **66**, 102-110, 2016.

The overall efficacy and safety profile of a new drug is partially evaluated by the therapeutic index in clinical studies and by the protective index (PI) in preclinical studies. In-silico predictive methods may facilitate the assessment of these indicators. Although QSAR and QSTR models can be used for predicting PI, their predictive capability has not been evaluated. To test this capability, we developed QSAR and QSTR models for predicting the activity and toxicity of anticonvulsants at accuracy levels above the literature-reported threshold (LT) of good QSAR models as tested by both the internal 5-fold cross validation and external validation method.

Analyzing the substitution effect on the CoMFA results within the framework of density functional theory (DFT)

Alejandro Morales-Bayuelo [Universidad de Talca]

J. Mol.Mod., **22**, 164, 2016.

Though QSAR was originally developed in the context of physical organic chemistry, it has been applied very extensively to chemicals (drugs) which act on biological systems, in this idea one of the most important QSAR methods is the 3D QSAR model. However, due to the complexity of understanding the results it is necessary to postulate new methodologies to highlight their physical-chemical meaning. In this sense, this work postulates new insights to understand the CoMFA results using molecular quantum similarity and chemical reactivity descriptors within the framework of density functional theory.

Potentials and Parameters

Assessing the accuracy of improved force-matched water models derived from Ab initio molecular dynamics simulations

Andreas Köster, Thomas Spura, Gábor Rutkai, Jan Kessler, Hendrik Wiebeler, Jadran Vrabec and Thomas D. Kühne [University of Paderborn]

J. Comp. Chem., **37**, 1828–1838, 2016.

The accuracy of water models derived from ab initio molecular dynamics simulations by means on an improved force-matching scheme is assessed for various thermodynamic, transport, and structural properties. It is found that although the resulting force-matched water models are typically less accurate than fully empirical force fields in predicting thermodynamic properties, they are nevertheless much more accurate than generally appreciated in reproducing the structure of liquid water and in fact superseding most of the commonly used empirical water models.

Potentials and Parameters (Cont'd)

Parametrization of Chain Molecules in Dissipative Particle Dynamics

Ming-Tsung Lee, Runfang Mao, Aleksey Vishnyakov, and Alexander V. Neimark [The State University of New Jersey]

J. Phys. Chem. B., **120**, 4980–4991, 2016.

This paper presents a consistent strategy for parametrization of coarse-grained models of chain molecules in dissipative particle dynamics (DPD), where the soft-core DPD interaction parameters are fitted to the activities in solutions of reference compounds that represent different fragments of target molecules. The intercomponent parameters are matched either to the infinite dilution activity coefficients in binary solutions or to the solvent activity in polymer solutions. The respective calibration relationships between activity and intercomponent interaction parameter are constructed from the results of Monte Carlo simulation of the coarse-grained solutions of reference compounds.

Molecular Dynamics

Collision-Induced Dissociation of Electrosprayed Protein Complexes: An All-Atom Molecular Dynamics Model with Mobile Protons

Vlad Popa, Danielle A. Trecroce, Robert G. McAllister, and Lars Konermann [The University of Western Ontario]

J. Phys. Chem. B., **120**, 5114–5124, 2016.

Electrospray ionization mass spectrometry (ESI-MS) has become an indispensable technique for examining noncovalent protein complexes. Collision-induced dissociation (CID) of these multiply protonated gaseous ions usually culminates in ejection of a single subunit with a disproportionately large amount of charge. Experiments suggest that this process involves subunit unfolding prior to separation from the residual complex, as well as H⁺ migration onto the unravelling chain. Molecular dynamics (MD) simulations are a promising avenue for gaining detailed insights into these CID events.

Comprehensive analysis of motions in molecular dynamics trajectories of the actin capping protein and its inhibitor complexes

Ryotaro Koike, Shuichi Takeda, Yuichiro Maéda and Motonori Ota [Nagoya University, Furo-cho]

Proteins: Stru. Fun. & Bioinf., **84**, 948–956, 2016.

The actin capping protein (CP) binds to actin filaments to block further elongation. The capping activity is inhibited by proteins V-1 and CARMIL interacting with CP via steric and allosteric mechanisms, respectively. The crystal structures of free CP, CP/V-1, and CP/CARMIL complexes suggest that the binding of CARMIL alters the flexibility of CP rather than the overall structure of CP, and this is an allosteric inhibition mechanism. Here, we performed molecular dynamics (MD) simulations of CP in the free form, and in complex with CARMIL or V-1. The resulting trajectories were analyzed exhaustively using Motion Tree, which identifies various rigid-body motions ranging from small local motions to large domain motions.

Free Energy Perturbation

Alchemical Free Energy Calculations and Isothermal Titration Calorimetry Measurements of Aminoadamantanes Bound to the Closed State of Influenza A/M2TM

Harris Ioannidis, Antonios Drakopoulos, Christina Tzitzoglaki, Nadine Homeyer, Felix Kolarov, Paraskevi Gkeka, Kathrin Freudenberger, Christos Liolios, Günter Gauglitz, Zoe Cournia, Holger Gohlke, and Antonios Kolocouris [National and Kapodistrian University of Athens]

J.Chem. Infor. and Mod., **56**, 862–876, 2016.

Adamantane derivatives, such as amantadine and rimantadine, have been reported to block the transmembrane domain (TM) of the M2 protein of influenza A virus (A/M2) but their clinical use has been discontinued due to evolved resistance in humans. Although experiments and simulations have provided adequate information about the binding interaction of amantadine or rimantadine to the M2 protein, methods for predicting binding affinities of whole series of M2 inhibitors have so far been scarcely applied. Here we show that alchemical free energy calculations of ligand binding using the Bennett acceptance ratio (BAR) method are valuable for determining the relative binding potency of A/M2 inhibitors of the aminoadamantane type covering a binding affinity range of only ~ 2 kcal mol⁻¹.

QM and QM/MM

CPMD/GULP QM/MM interface for modeling periodic solids: Implementation and its application in the study of Y-zeolite supported Rh_n clusters

Sudhir K. Sahoo and Nisanth N. Nair [Indian Institute of Technology, Kanpur]

J. Comp. Chem., **37**, 1657–1667, 2016.

We report here the development of hybrid quantum mechanics/molecular mechanics (QM/MM) interface between the plane-wave density functional theory based CPMD code and the empirical force-field based GULP code for modeling periodic solids and surfaces. The hybrid QM/MM interface is based on the electrostatic coupling between QM and MM regions. The interface is designed for carrying out full relaxation of all the QM and MM atoms during geometry optimizations and molecular dynamics simulations, including the boundary atoms.

Methodological aspects of QM/MM calculations: A case study on matrix metalloproteinase-2

Tatiana Vasilevskaya, Maria G. Khrenova, Alexander V. Nemukhin and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Comp. Chem., **37**, 1801–1809, 2016.

We address methodological issues in quantum mechanics/molecular mechanics (QM/MM) calculations on a zinc-dependent enzyme. We focus on the first stage of peptide bond cleavage by matrix metalloproteinase-2 (MMP-2), that is, the nucleophilic attack of the zinc-coordinating water molecule on the carbonyl carbon atom of the scissile fragment of the substrate. This step is accompanied by significant charge redistribution around the zinc cation, bond cleavage, and bond formation. We vary the size and initial geometry of the model system as well as the computational protocol to demonstrate the influence of these choices on the results obtained.

QM and QM/MM (Cont'd)

Multipole moments for embedding potentials: Exploring different atomic allocation algorithms

Morten S. Nørby [University of Southern Denmark], Jógvan Magnus Haugaard Olsen, Jacob Kongsted and Hans Jørgen Aagard Jensen

J. Comp. Chem., **37**, 1887–1896, 2016.

Polarizable quantum mechanical (QM)/molecular mechanics (MM)-embedding methods are currently among the most promising methods for computationally feasible, yet reliable, production calculations of localized excitations and molecular response properties of large molecular complexes, such as proteins and RNA/DNA, and of molecules in solution. Our aim is to develop a computational methodology for distributed multipole moments and their associated multipole polarizabilities which is accurate, computationally efficient, and with smooth convergence with respect to multipole order.

Effects of ionization on stability of 1-methylcytosine — DFT and PCM studies

Ewa D. Raczynska, Piotr Michalec, Marcin Zalewski, Mariusz Sapuła [Interdisciplinary Department of Biotechnology, Warszawa]

J. Mol.Mod., **22**, 146, 2016.

Consequences of ionization were studied by quantum-chemical methods (DFT and PCM) for 1-methylcytosine (**MC**)—a model of the nucleobase cytosine (**C**) connected with sugar in DNA. For calculations, three prototropic tautomers (one amino and two imino forms) and two imino zwitterions were considered, including conformational or configurational isomerism of exo heterogroups. Ionization and interactions between neighboring groups affect intramolecular proton-transfers, geometric and thermodynamic parameters, and electron delocalization for individual isomers.

Ambient-Potential Composite Ewald Method for ab Initio Quantum Mechanical/Molecular Mechanical Molecular Dynamics Simulation

Timothy J. Giese and Darrin M. York [Rutgers University, Piscataway]

J. Chem. Theor. and Comp., **12**, 2611–2632, 2016.

A new approach for performing Particle Mesh Ewald in ab initio quantum mechanical/molecular mechanical (QM/MM) simulations with extended atomic orbital basis sets is presented. The new approach, the Ambient-Potential Composite Ewald (CEw) method, does not perform the QM/MM interaction with Mulliken charges nor electrostatically fit charges. Instead the nuclei and electron density interact directly with the MM environment, but in a manner that avoids the use of dense Fourier transform grids. By performing the electrostatics with the underlying QM density, the CEw method avoids self-consistent field instabilities that have been encountered with simple charge mapping procedures.

A Projector-Embedding Approach for Multiscale Coupled-Cluster Calculations Applied to Citrate Synthase

Simon J. Bennie, Marc W. van der Kamp, Robert C. R. Pennifold, Martina Stella, Frederick R. Manby, and Adrian J. Mulholland [University of Bristol]

J. Chem. Theor. and Comp., **12**, 2689–2697, 2016.

Projector-based embedding has recently emerged as a robust multiscale method for the calculation of various electronic molecular properties. We present the coupling of projector embedding with quantum mechanics/molecular mechanics modeling and apply it for the first time to an enzyme-catalyzed reaction. Using projector-based embedding, we combine coupled-cluster theory, density-functional theory (DFT), and molecular mechanics to compute energies for the proton abstraction from acetyl-coenzyme A by citrate synthase.

QM and QM/MM (Cont'd)

New Insights on the Mechanism of Cyclization in Chromophore Maturation of Wild-Type Green Fluorescence Protein: A Computational Study

Yingying Ma, Hao Zhang, Qiao Sun, and Sean C. Smith [The University of New South Wales]

J. Phys. Chem. B., **120**, 5386–5394, 2016.

Cyclization is the first step in the chromophore maturation process of the green fluorescent protein (GFP). In our previous paper [*J. Phys. Chem. B* **2012**, 116, 1426–1436], the results of molecular dynamics simulation suggested the possibility that the amide nitrogen atom of Gly67 attacks the carbonyl carbon of Ser65 directly to complete the cyclization process (one-step mechanism). In this paper, density functional theory (DFT) and quantum mechanical/molecular mechanical (QM/MM) calculations were undertaken to study this step reaction in detail. Three cluster model systems (model A, model B, and model C) and large protein system were set up to investigate the cyclization process.

Comparative or Homology Modeling

CMsearch: simultaneous exploration of protein sequence space and structure space improves not only protein homology detection but also protein structure prediction

Xuefeng Cui, Zhiwu Lu, Sheng Wang, Jim Jing-Yan Wang, and Xin Gao [], Computational Bioscience Research Center (CBRC), Thuwal]

Bioinformatics. **32**, i332-i340, 2016.

Protein homology detection, a fundamental problem in computational biology, is an indispensable step toward predicting protein structures and understanding protein functions. Despite the advances in recent decades on sequence alignment, threading and alignment-free methods, protein homology detection remains a challenging open problem. We present a novel network-based protein homology detection method, CMsearch, based on cross-modal learning. Instead of exploring a single network built from the mixture of sequence and structure space information, CMsearch builds two separate networks to represent the sequence space and the structure space.

Ligand Docking

Structural insights into the interactions of phorbol ester and bryostatin complexed with protein kinase C: a comparative molecular dynamics simulation study

Patcharapong Thangsunan, Suriya Tateing, Supa Hannongbua & Nuttee Suree Chiang Mai University]

J. Biomol. Stru. and Dyn., **34**, 1561-1575, 2016.

Protein kinase C (PKC) isozymes are important regulatory enzymes that have been implicated in many diseases, including cancer, Alzheimer's disease, and in the eradication of HIV/AIDS. Given their potential clinical ramifications, PKC modulators, e.g. phorbol esters and bryostatin, are also of great interest in the drug development. Here, we report the first comparative molecular dynamics study aimed at gaining structural insight into the mechanisms by which the PKC delta cys2 activator domain is used in its binding to phorbol ester and bryostatin-1.

Ligand Docking (Cont'd)

BIM (BCL-2 interacting mediator of cell death) SAHB (stabilized α helix of BCL2) not always convinces BAX (BCL-2-associated X protein) for apoptosis

Sharad Verma, Sukriti Goyal, Chetna Tyagi, Salma Jamal, Aditi Singh, Abhinav Grover [Jawaharlal Nehru University]

J. Mol.Graph. and Mod., **66**, 94-101, 2016.

The interaction of BAX (BCL-2-associated X protein) with BIM (BCL-2 interacting mediator of cell death) SAHB (stabilized α helix of BCL2) directly initiates BAX-mediated mitochondrial apoptosis. This molecular dynamics study reveals that BIM SAHB forms a stable complex with BAX but it remains in a non-functional conformation. N terminal of BAX folds towards the core which has been reported exposed in the functional monomer. The $\alpha 1$ - $\alpha 2$ loop, which has been reported in open conformation in functional BAX, acquires a closed conformation during the simulation.

The tertiary structures of porcine AhR and ARNT proteins and molecular interactions within the TCDD/AhR/ARNT complex

Karina Orlowska, Tomasz Molcan, Sylwia Swigonska, Agnieszka Sadowska, Monika Jablonska, Anna Nynca, Jan P. Jastrzebski, Renata E. Ciereszko [University of Warmia and Mazury]

J. Mol.Graph. and Mod., **66**, 119-126, 2016.

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that can be activated by structurally diverse synthetic and natural chemicals, including toxic environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In the present study, homology models of the porcine AhR-ligand binding domain (LBD) and the porcine aryl hydrocarbon receptor nuclear translocator-ligand binding domain (ARNT-LBD) were created on the basis of structures of closely related respective proteins i.e., human Hif-2 α and ARNT.

Benzothiazole Derivative as a Novel Mycobacterium tuberculosis Shikimate Kinase Inhibitor: Identification and Elucidation of Its Allosteric Mode of Inhibition

Rukmankesh Mehra, Vikrant Singh Rajput, Monika Gupta, Reena Chib, Amit Kumar, Priya Wazir, Inshad Ali Khan, and Amit Nargotra [CSIR-Indian Institute of Integrative Medicine]

J.Chem. Infor. and Mod., **56**, 930-940, 2016.

Mycobacterium tuberculosis shikimate kinase (Mtb-SK) is a key enzyme involved in the biosynthesis of aromatic amino acids through the shikimate pathway. Since it is proven to be essential for the survival of the microbe and is absent from mammals, it is a promising target for anti-TB drug discovery. In this study, a combined approach of in silico similarity search and pharmacophore building using already reported inhibitors was used to screen a procured library of 20,000 compounds of the commercially available ChemBridge database.

Prediction of Protein-Ligand Binding Poses via a Combination of Induced Fit Docking and Metadynamics Simulations

Anthony J. Clark, Pratyush Tiwary [Columbia University, New York], Ken Borrelli, Shulu Feng, Edward B. Miller, Robert Abel, Richard A. Friesner, and B. J. Berne

J. Chem. Theor. and Comp., **12**, 2990-2998, 2016.

Ligand docking is a widely used tool for lead discovery and binding mode prediction based drug discovery. The greatest challenges in docking occur when the receptor significantly reorganizes upon small molecule binding, thereby requiring an induced fit docking (IFD) approach in which the receptor is allowed to move in order to bind to the ligand optimally. IFD methods have had some success but suffer from a lack of reliability. Complementing IFD with all-atom molecular dynamics (MD) is a straightforward solution in principle but not in practice due to the severe time scale limitations of MD.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 67, June, 2016.

- 1-13 **Computational docking, molecular dynamics simulation and subsite structure analysis of a maltogenic amylase from *Bacillus lehensis* G1 provide insights into substrate and product specificity**, Nor Hasmaliana Abdul Manas, Farah Diba Abu Bakar, Rosli Md. Illias [Universiti Teknologi Malaysia]

See Applications / Enzyme Catalysis.

- 14-19 **DFT study of zigzag (n, 0) single-walled carbon nanotubes: ^{13}C NMR chemical shifts**, Teobald Kupka, Michal Stachów, Leszek Stobiński, Jakub Kaminský [Academy of Sciences of the Czech Republic]

^{13}C NMR chemical shifts of selected finite-size models of pristine zigzag single walled carbon nanotubes (SWCNTs) with a diameter of $\sim 0.4\text{--}0.8$ nm and length up to 2.2 nm were studied theoretically. Results for finite SWCNTs models containing 1, 4 and 10 adjacent bamboo-type units were compared with data obtained for infinite tubes in order to estimate the reliability of small finite models in predicting magnetic properties of real-size nanotubes and to assess their tube-length dependence.

- 20-32 **Insights into RpoB clinical mutants in mediating rifampicin resistance in *Mycobacterium tuberculosis***, Ameeruddin Nusrath Unissa [National Institute for Research in Tuberculosis, India], Sameer Hassan, Venkatesan Indira Kumari, Ravi Revathy, Luke Elizabeth Hanna

Rifampicin (RIF) an essential first-line anti-tuberculosis (TB) drug, resistance to RIF is a potential threat to TB control program and widely considered as surrogate marker for detection of multi-drug resistant-TB (MDR-TB), molecular understanding of which is the utmost need of the hour. In the present study, models of wild type (WT) and seven MTs (D516V, L521M, H526D, H526R, H526Y, S531L and L533P) of RpoB from MTB were generated using crystal structure of 2A68 and 4KBM as templates, for deducing 3 domains structure.

- 33-43 **Discerning the catalytic mechanism of *Staphylococcus aureus* sortase A with QM/MM free energy calculations**, Pooja Shrestha, Jeff Wereszczynski [Illinois Institute of Technology]

See Applications / Enzyme Catalysis.

- 44-53 **Visualizing ensembles in structural biology**, Ryan L. Melvin, Freddie R. Salsbury Jr. [Wake Forest University]

Displaying a single representative conformation of a biopolymer rather than an ensemble of states mistakenly conveys a static nature rather than the actual dynamic personality of biopolymers. However, there are few apparent options due to the fixed nature of print media. Here we suggest a standardized methodology for visually indicating the distribution width, standard deviation and uncertainty of ensembles of states with little loss of the visual simplicity of displaying a single representative conformation.

- 54-61 **Influence of density and environmental factors on decomposition kinetics of amorphous polylactide – Reactive molecular dynamics studies**, A. Mlyniec [AGH University of Science and Technology], M. Ekiert, A. Morawska-Chochol, T. Uhl

In this work, we investigate the influence of the surrounding environment and the initial density on the decomposition kinetics of polylactide (PLA). The decomposition of the amorphous PLA was investigated by means of reactive molecular dynamics simulations. A computational model simulates the decomposition of PLA polymer inside the bulk, due to the assumed lack of removal of reaction products from the polymer matrix.

- 62-68 **pH effects on adsorption behavior and self-aggregation of dodecylamine at muscovite/aqueous interfaces**, Li Wang, Runqing Liu, Yuehua Hu, Wei Sun [Central South University Changsha]

See Applications / Protein Dynamics.

- 69-84 **Mechanisms of histone lysine-modifying enzymes: A computational perspective on the role of the protein environment**, Wilian Augusto Cortopassi, Kiran Kumar, Fernanda Duarte, Andre Silva Pimentel, Robert S. Paton [Chemistry Research Laboratory, 12 Mansfield Road, Oxford]

See Applications / Protein Dynamics.

- 85-93 **A theoretical study of π -stacking interactions in C-substituted tetrazoles**, Abdolkarim Farrokhzadeh, Ali Reza Modarresi-Alam [University of Sistan and Baluchestan], Farideh Badichi Akher, Ali Ebrahimi

The π -stacking effects of benzene ring (Ben) with 1H- and 2H-tetrazole derivatives (1H-TZ-X and 2H-TZ-X) substituted at C5 (where X is Cl, COH, NO, NO₂, CN, NH₂, OH, OCH₃, SH and H) has been investigated by the quantum mechanical calculations at the M06-2X/6-311++G** level.

- 94-101 **BIM (BCL-2 interacting mediator of cell death) SAHB (stabilized α helix of BCL2) not always convinces BAX (BCL-2-associated X protein) for apoptosis**, Sharad Verma, Sukriti Goyal, Chetna Tyagi, Salma Jamal, Aditi Singh, Abhinav Grover [Jawaharlal Nehru University]

See Methodology / Ligand Docking.

- 102-110 **Towards cheminformatics-based estimation of drug therapeutic index: Predicting the protective index of anticonvulsants using a new quantitative structure-index relationship approach**, Shangying Chen, Peng Zhang, Xin Liu, Chu Qin, Lin Tao, Cheng Zhang, Sheng Yong Yang, Yu Zong Chen, Wai Keung Chui [National University of Singapore]

See Methodology / QSAR.

- 111-118 **Second-order nonlinear optical responses of carboranyl-substituted indole/indoline derivatives: impact of different substituents**, Hong-Qiang Wang, Wen-Yong Wang, Xin-Yan Fang, Li Wang, Chang-Li Zhu, Zhen-Zhen Chen, He Chen, Yong-Qing Qiu [Northeast Normal University]

Carborane has been the subject of great interest over the last decades due to its high structural, chemical, biological stability and diverse applications. In the present work, carboranyl-substituted indole/indoline compounds and their functionalized derivatives have been systematically investigated by density functional theory (DFT) method with the view of assessing their electronic structures and first hyperpolarizabilities.

- 119-126 **The tertiary structures of porcine AhR and ARNT proteins and molecular interactions within the TCDD/AhR/ARNT complex**, Karina Orlowska, Tomasz Molcan, Sylwia Swigonska, Agnieszka Sadowska, Monika Jablonska, Anna Nynca, Jan P. Jastrzebski, Renata E. Ciereszko [University of Warmia and Mazury]

See Methodology / Ligand Docking.

- 127-136 **Arylhydrazone derivatives of naproxen as new analgesic and anti-inflammatory agents: Design, synthesis and molecular docking studies**, Homa Azizian, Zahra Mousavi, Hamidreza Faraji, Mohammad Tajik, Kowsar Bagherzadeh, Peyman Bayat, Abbas Shafiee, Ali Almasirad [Islamic Azad University]

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 37 (18), July, 2016.

- 1657–1667 **CPMD/GULP QM/MM interface for modeling periodic solids: Implementation and its application in the study of Y-zeolite supported Rh_n clusters**, Sudhir K. Sahoo and Nisanth N. Nair [Indian Institute of Technology, Kanpur]

See Methodology / QM and QM/MM.

- 1668–1671 **pKa prediction for acidic phosphorus-containing compounds using multiple linear regression with computational descriptors**, Donghai Yu, Ruobing Du and Ji-Chang Xiao [Shanghai Institute of Organic Chemistry]

Ninety-six acidic phosphorus-containing molecules with pK_a 1.88 to 6.26 were collected and divided into training and test sets by random sampling. Structural parameters were obtained by density functional theory calculation of the molecules.

- 1672–1680 **Insights on selenium and tellurium diaryldichalcogenides: A benchmark DFT study** Francesco Zaccaria, Lando P. Wolters, Célia Fonseca Guerra and Laura Orian [Università Studi Di Padova]

Selenium based diaryl dichalcogenides are compounds that are receiving attention in organic synthesis as eco-friendly oxidation agents as well as in pharmaceutical chemistry, where, together with tellurium-based derivatives, are appealing drugs mainly for their antioxidant properties. A benchmark study to establish optimal density functional theory (DFT) methods for the description of their molecular and electronic structure as well as for their energetics is presented here.

- 1681–1696 **Protein environmental effects on iron-sulfur clusters: A set of rules for constructing computational models for inner and outer coordination spheres**, Travis V. Harris and Robert K. Szilagyi [Montana State University, Bozeman]

See Applications / Protein Dynamics.

- 1697–1703 **Modeling a halogen dance reaction mechanism: A density functional theory study**, Leighton Jones and Benjamin J. Whitaker [University of Leeds]

Since the discovery of the halogen dance (HD) reaction more than 60 years ago, numerous insights into the mechanism have been unveiled. To date however, the reaction has not been investigated from a theoretical perspective. Density functional theory (DFT) was used to model the potential energy surface linking the starting reagents to the lithiated products for each step in the mechanism using a thiophene substrate.

- 1704–1710 **Analysis of the bond-valence method for calculating ^{29}Si and ^{31}P magnetic shielding in covalent network solids**, Sean T. Holmes, Fahri Alkan, Robbie J. Iuliucci, Karl T. Mueller and Cecil Dybowski [University of Delaware, Newark]

^{29}Si and ^{31}P magnetic-shielding tensors in covalent network solids have been evaluated using periodic and cluster-based calculations. The cluster-based computational methodology employs pseudoatoms to reduce the net charge (resulting from missing co-ordination on the terminal atoms) through valence modification of terminal atoms using bond-valence theory (VMTA/BV).

- 1711–1724 **Rapid approximate calculation of water binding free energies in the whole hydration domain of (bio)macromolecules**, Maria M. Reif and Martin Zacharias [Technische Universität München]

See Applications / Free Energy Calculations.

- 1725–1733 **Necessity of high-resolution for coarse-grained modeling of flexible proteins**, Zhiguang Jia and Jianhan Chen [Kansas State University, Manhattan]

See Applications / Protein Folding.

Journal of Computational Chemistry, 37 (19), July, 2016.

- 1753–1765 **Electron correlation in the interacting quantum atoms partition via coupled-cluster lagrangian densities**, Fernando José Holguín-Gallego, Rodrigo Chávez-Calvillo, Marco García-Revilla, Evelio Francisco, Ángel Martín Pendás and Tomás Rocha-Rinza [Ciudad Universitaria]

The electronic energy partition established by the Interacting Quantum Atoms (IQA) approach is an important method of wavefunction analyses which has yielded valuable insights about different phenomena in physical chemistry. We have implemented the IQA energy partition based on CC Lagrangian one- and two-electron orbital density matrices.

- 1766–1780 **Interactions of the “piano-stool” [ruthenium(II)(η^6 -arene)(quinolone)Cl] $^+$ complexes with water; DFT computational study**, Tereza Zábajníková, Radim Cajzl, Jakob Kljun, Zdeněk Chval, Iztok Turel and Jaroslav V. Burda [Charles University, Prague 2]

Full optimizations of stationary points along the reaction coordinate for the hydration of several quinolone Ru(II) half-sandwich complexes were performed in water environment using the B3PW91/6-31+G(d)/PCM/UAKS method.

- 1781–1793 **Comparing three stochastic search algorithms for computational protein design: Monte Carlo, replica exchange Monte Carlo, and a multistart, steepest-descent heuristic**, David Mignon and Thomas Simonson [Ecole Polytechnique, Palaiseau]

See Applications / Protein Design.

- 1794–1800 **Chemical potential and reaction electronic flux in symmetry controlled reactions**, Stefan Vogt-Geisse [Universidad De Concepción] and Alejandro Toro-Labbé

In symmetry controlled reactions, orbital degeneracies among orbitals of different symmetries can occur along a reaction coordinate. We propose a new way for the calculation of the chemical potential based on a many orbital approach, suitable for reactions in which symmetry is preserved.

- 1801–1809 **Methodological aspects of QM/MM calculations: A case study on matrix metalloproteinase-2**, Tatiana Vasilevskaya, Maria G. Khrenova, Alexander V. Nemukhin and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

See Methodology / QM and QM/MM.

- 1810–1818 **Improved free energy profile for reduction of NO in cytochrome c dependent nitric oxide reductase (cNOR)**, Margareta R. A. Blomberg [Stockholm University] and Per E. M. Siegbahn

See Applications / Enzyme Catalysis.

- 1819–1827 **Reformulating the entropic contribution in molecular docking scoring functions**, Piero Procacci [University of Florence, Italy]

We have derived, in the context of the Rigid Rotor Harmonic Approximation (RRHO), a general mass and Planck's constant h independent expression for the dissociation free energy in ligand–receptor systems, featuring a systematically (anti-binding) additive negative entropic term depending on readily available ligand–receptor quantities.

- 1828–1838 **Assessing the accuracy of improved force-matched water models derived from Ab initio molecular dynamics simulations**, Andreas Köster, Thomas Spura, Gábor Rutkai, Jan Kessler, Hendrik Wiebeler, Jadran Vrabec and Thomas D. Kühne [University of Paderborn]

See Methodology / Potentials and Parameters.

- 1839–1846 **Sodium chloride's effect on self-assembly of diphenylalanine bilayer**, Junpyo Kwon, Myeongsang Lee and Sungsoo Na [Korea University, Seoul]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

Journal of Computational Chemistry, 37 (20), July, 2016.

- 1861–1865 **Ranking protein–protein docking results using steered molecular dynamics and potential of mean force calculations**, Laura J. Kingsley, Juan Esquivel-Rodríguez, Ying Yang, Daisuke Kihara and Markus A. Lill [Purdue University, West Lafayette]

See Applications / Protein - Protein Interactions.

- 1866–1875 **Quantum Monte Carlo with very large multideterminant wavefunctions**, Anthony Scemama, Thomas Applencourt, Emmanuel Giner and Michel Caffarel [CNRS-Université De Toulouse]

An algorithm to compute efficiently the first two derivatives of (very) large multideterminant wavefunctions for quantum Monte Carlo calculations is presented. The calculation of determinants and their derivatives is performed using the Sherman–Morrison formula for updating the inverse Slater matrix.

- 1876–1886 **On the nature of interactions in the $\text{F}_2\text{OXe}\cdots\text{NCCH}_3$ complex: Is there the $\text{Xe(IV)}-\text{N}$ bond?**, Emilia Makarewicz, Jan Lundell, Agnieszka J. Gordon and Slawomir Berski [University of Wroclaw]

Nature of the bonding in isolated XeOF_2 molecule and $\text{F}_2\text{OXe}\cdots\text{NCCH}_3$ complexes have been studied in the gas phase (0 K) using Quantum Chemical Topology methods. The wave functions have been approximated at the MP2 and DFT levels of calculations, using the APFD, B3LYP, M062X, and B2PLYP functionals with the GD3 dispersion correction.

- 1887–1896 **Multipole moments for embedding potentials: Exploring different atomic allocation algorithms**, Morten S. Nørby [University of Southern Denmark], Jógvan Magnus Haugaard Olsen, Jacob Kongsted and Hans Jørgen Aagard Jensen

See Methodology / QM and QM/MM.

- 1897–1906 **Compressing molecular dynamics trajectories: Breaking the one-bit-per-sample barrier**, Jan Huwald [Friedrich Schiller University], Stephan Richter, Bashar Ibrahim and Peter Dittrich

Molecular dynamics simulations yield large amounts of trajectory data. For their durable storage and accessibility an efficient compression algorithm is paramount. State of the art domain-specific algorithms combine quantization, Huffman encoding and occasionally domain knowledge. We propose the high resolution trajectory compression scheme (HRTC) that relies on piecewise linear functions to approximate quantized trajectories.

- 1907–1913 **Structural interconnections and the role of heptagonal rings in endohedral trimetallic nitride template fullerenes**, Li-Hua Gan, Dan Lei and Patrick W. Fowler [Sheffield University]

Recent experiments indicate that fullerene isomers outside the classical definition can also encapsulate metallic atoms or clusters to form endohedral metallofullerenes. Our systematic study using DFT calculations, suggests that many heptagon-including nonclassical trimetallic nitride template fullerenes are similar in stability to their classical counterparts, and that conversion between low-energy nonclassical and classical parent cages via Endo–Kroto insertion/extrusion of C_2 units and Stone–Wales isomerization may facilitate the formation of endohedral trimetallic nitride fullerenes.

- 1914–1923 **Quantum chemical study of the autoxidation of ascorbate**, Nils Herrmann, Norah Heinz, Michael Dolg and Xiaoyan Cao [University of Cologne]

Reactions involved in the autoxidation of ascorbate have been investigated with quantum chemical first-principles and ab initio methods. Reaction energies and Gibbs energies of the reactions were calculated at the density functional theory level applying the gradient-corrected BP86 and the hybrid B3LYP functionals together with def2-TZVP basis sets.

- 1924–1934 **Theoretical study of lithium ionic conductors by electronic stress tensor density and electronic kinetic energy density**, Hiroo Nozaki, Yosuke Fujii, Kazuhide Ichikawa, Taku Watanabe, Yuichi Aihara and Akitomo Tachibana [Kyoto University]

We analyze the electronic structure of lithium ionic conductors, Li_3PO_4 and Li_3PS_4 , using the electronic stress tensor density and kinetic energy density with special focus on the ionic bonds among them.

- 1935–1946 **Multistate empirical valence bond study of temperature and confinement effects on proton transfer in water inside hydrophobic nanochannels**, Amani Tahat and Jordi Martí [Technical University of Catalonia-Barcelona Tech]

Microscopic characteristics of an aqueous excess proton in a wide range of thermodynamic states, from low density amorphous ices (down to 100 K) to high temperature liquids under the critical point (up to 600 K), placed inside hydrophobic graphene slabs at the nanometric scale (with interplate distances between 3.1 and 0.7 nm wide) have been analyzed by means of molecular dynamics simulations.

Journal of Molecular Modeling, 22 (7), July, 2016.

- 164 **Analyzing the substitution effect on the CoMFA results within the framework of density functional theory (DFT)**, Alejandro Morales-Bayuelo [Universidad de Talca]

See Methodology / QSAR.

- 163 **Structure-based virtual screening of hypothetical inhibitors of the enzyme longiborneol synthase—a potential target to reduce Fusarium head blight disease**, E. Bresso, V. Leroux, M. Urban, K. E. Hammond-Kosack, B. Maigret, N. F. Martins [Biotechnology Parque Estação Biológica - PqEB]

See Applications / Medicinal Chemistry and Drug Design.

- 162 **Gibbs ensemble Monte Carlo simulation using an optimized potential model: pure acetic acid and a mixture of it with ethylene**, Minhua Zhang, Lihang Chen, Huaming Yang, Xijiang Sha, Jing Ma [Tianjin University]

Gibbs ensemble Monte Carlo simulation with configurational bias was employed to study the vapor–liquid equilibrium (VLE) for pure acetic acid and for a mixture of acetic acid and ethylene.

- 161 **Fullerenes and their derivatives as inhibitors of tumor necrosis factor- α with highly promoted affinities**, Gaoyin Wu, Xuejiao J. Gao, Joonkyung Jang, Xingfa Gao [Chinese Academy of Sciences]

See Applications / Medicinal Chemistry and Drug Design.

- 160 **Transition metal doped ZnO nanoclusters for carbon monoxide detection: DFT studies**, Saeed Aslanzadeh [Technical Vocational University, Tehran]

Metal doped ZnO nanomaterials have attracted considerable attention as a chemical sensor for toxic gases. Here, the electronic sensitivity of pristine and Sc-, Ti-, V-, Cr-, Mn-, and Fe-doped Zn₁₂O₁₂ nanoclusters toward CO gas is investigated using density functional theory calculations.

- 159 **Computing thermomechanical properties of dry homopolymers used as raw materials for formulation of biomedical hydrogels**, Pavlo Demianenko, Benoît Minisini [ISMANS, Avenue Frédéric Auguste Bartholdi], Gabriel Ortell, Mouad Lamrani, Fabienne Poncin-Epaillard

Different static properties have been calculated with COMPASS force field for polyacrylamide, poly(2-hydroxyethylacrylate) (HEA), poly(2-hydroxyethylmethacrylate) (HEMA), poly(glycidylmethacrylate) (GMA), polyethylene glycol (PEG), and poly(2,2,2-trifluoroethylmethacrylate) (TFEM). For each polymers, the calculated values were averaged on five equilibrated configurations of amorphous cell composed of one atactic chain containing 100 repeat units.

- 158 **A mechanistic investigation on the formation and rearrangement of silaspiropentane: A theoretical study**, Cem Burak Yildiz [University of Aksaray, Aksaray], Akin Azizoglu

The formation of silaspiropentane from addition of singlet silacyclopropylidene **1** and silacyclopropylidenoid **8** to ethylene has been investigated separately at the B3LYP, X3LYP, WB97XD, and M05-2X theories using the 6-31+G(d,p) basis set.

- 157 **Binuclear rhenium carbonyl nitrosyls related to dicobalt octacarbonyl and their decarbonylation products**, Bing Xu, Qian-Shu Li, Yaoming Xie, R. Bruce King [University of Georgia, Athens]

The geometries and thermochemistry of Re₂(NO)₄(CO)_n (n=4, 3, 2, 1, 0) structures isovalent with the binuclear cobalt carbonyls Co₂(CO)_{n+4} have been examined using density functional theory.

- 156 **Metal binding mediated conformational change of XPA protein: a potential cytotoxic mechanism of nickel in the nucleotide excision repair**, Jianping Hu, Ziheng Hu, Yan Zhang, Xiaojun Gou, Ying Mu, Lirong Wang, Xiang-Qun Xie [University of Pittsburgh]

See Applications / Nucleic Acids.

- 155 **Non-bonding interactions and non-covalent delocalization effects play a critical role in the relative stability of group 12 complexes arising from interaction of diethanoldithiocarbamate with the cations of transition metals Zn(II), Cd(II), and Hg(II): a theoretical study**, Homayoon Bahrami, Saeed Farhadi [Lorestan University], Firouzeh Siadatnasab

The chelating properties of diethanoldithiocarbamate (DEDC) and π -electron flow from the nitrogen atom to the sulfur atom via a plane-delocalized π -orbital system (quasi ring) was studied using a density functional theory method.

- 154 **Computer-simulation-based selection of optimal monomer for imprinting of tri-O-acetyl adenosine in a polymer matrix: calculations for benzene solution**, Ya. V. Douhaya, V. V. Barkaline [Belarusian National Technical University], A. Tsakalof

Molecular imprinting is a promising way to create polymer materials that can be used as artificial receptors, and have anticipated use in synthetic imitation of natural antibodies. In case of successful imprinting, the selectivity and affinity of the imprint for the substrate molecules are comparable with those of natural counterparts.

- 153 **Comparative theoretical kinetics and thermodynamics study on high-energy insensitive explosive 1,1-diamino-2,2-dinitroethene synthesis**, Min-Hsien Liu [Chung Cheng Institute of Technology], Chuan-Wen Liu

Two synthesis methods were investigated in this study in order to explore feasible reaction pathways to obtain the target DADNE product: (1) the nitration of tetrahalogen ethene and (2) the reaction of acetamidine hydrochloride with dicarbonyl dichloride.

- 152 **Theoretical insights into the properties of amino acid ionic liquids in aqueous solution**, Xueying Zhu, Hongqi Ai [University of Jinan, Jinan]

This report presents a systematic investigation of the interactions of water molecule(s) with a series of amino acid cations (Gly⁺, Ala⁺, Val⁺, and Leu⁺), halogen anions (Cl⁻, Br⁻, BF₄⁻, and PF₆⁻), and clusters (GlyCl)_n (n = 1–5). The results reveal that H-bonds between amino acid ionic liquids (AAILs) and water molecules are crucial to the properties of aqueous solution of AAILs.

- 151 **Cooperativity of intermolecular hydrogen bonds in microsolvated DMSO and DMF clusters: a DFT, AIM, and NCI analysis**, Natarajan Sathiyamoorthy Venkataramanan [SASTRA University, Thanjavur]

Density functional theory (DFT) calculations are performed to study the hydrogen-bonding in the DMSO-water and DMF-water complexes. Quantitative molecular electrostatic potential (MESP) and atoms-in-molecules (AIM) analysis are applied to quantify the relative complexation of DMSO and DMF with water molecules.

- 150 **Theoretical investigation of the addition reaction of the aluminum chlorosilylenoid H₂SiAlCl₃ with ethylene**, Mingxia Zhang, Wenzuo Li [Yantai University], Zhenbo Liu, Qingzhong Li, Jianbo Cheng

The addition reaction of the aluminum chlorosilylenoid H₂SiAlCl₃ with ethylene was investigated using the M06-2X and QCISD methods for the first time. The calculated results demonstrate that the addition reaction proceeds via two pathways: path I involves just one transition state, while path II involves two transition states.

- 149 **DFT-B3LYP study of interactions between host biphenyl-1-aza-18-crown-6 ether derivatives and guest Cd²⁺: NBO, NEDA, and QTAIM analyses**, R. Behjatmanesh-Ardakani, F. Pourroustaei-Ardakani, M. Taghdiri, Zahrabatoul Mosapour Kotena [University of Malaysia]

This report present the results of natural energy decomposition analysis (NEDA), natural bond orbital (NBO), and quantum theory of atoms in molecules (QTAIM) calculations of three derivatives of biphenyl-1-aza-18-crown-6 ether and their 1:1 complexes with Cd²⁺.

- 148 **Modeling prepolymerization step of a serotonin imprinted polymer**, Ersin Gündeğer, Cenk Selçuki, Burcu Okutucu [Ege University]

Studies on generating artificial macromolecular receptors by molecular imprinting of synthetic polymers significantly emerged in the literature during last decades. This study aims to investigate a serotonin imprinted polymer prepared by non-covalent approach using molecular modeling.

- 147 **Molecular dynamics study of the behavior of nitromethanes enclosed inside carbon nanotube containers**, Se Won Bae, Soo Gyeong Cho [Agency for Defense Development (ADD), Yuseong]

We utilized molecular dynamics (MD) to investigate the behavior of nitromethane molecules (NMs) enclosed inside carbon nanotube (CNT) containers sealed with buckybowls caps.

- 146 **Effects of ionization on stability of 1-methylcytosine — DFT and PCM studies**, Ewa D. Raczynska, Piotr Michalec, Marcin Zalewski, Mariusz Sapuła [Interdisciplinary Department of Biotechnology, Warszawa]

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Vol. 25, No. 6

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About 135 Papers from more than 30 Journals are cited.

1	APPLICATIONS (99)	Page 2		
1.1	Small Molecules (15)			
	Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 5
	QSAR	Page 5		
1.2	Biopolymers (82)			
	Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 16
	Protein Secondary Structure	Page 7	Enzyme Catalysis	Page 17
	Comparative or Homology Modeling	Page 7	Protein-Protein Interactions	Page 20
	Protein Side Chain Confirmationa and	Page 9	Membrane Proteins	Page 22
	Protein Conformational Analysis	Page 9	Protein Folding	Page 24
	Protein Structure Analysis	Page 11	Protein-Nucleic Acids	Page 25
	Protein Dynamics	Page 12	Nucleic Acids	Page 27
	Free Energy Calculations	Page 15		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 28		
2	METHODOLOGY (24)	Page 29		
	Potentials and Parameters	Page 29	QM & QM/MM	Page 31
	Molecular Dynamics	Page 29	Ligand Docking	Page 32
3	JOURNAL REVIEWS (7)	Page 36		
	Journal of Molecular Graphics and Modeling, 68, July, 2016.			
	Journal of Computational Chemistry, 37 (21, 22), August, 2016.			
	Journal of Computational Chemistry, 37 (23, 24), September, 2016			
	Journal of Molecular Modeling, 22 (8), August, 2016.			
	Journal of Molecular Modeling, 22 (9), September, 2016.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 51		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Discovery of New Anti-Schistosomal Hits by Integration of QSAR-Based Virtual Screening and High Content Screening

Bruno J. Neves, Rafael F. Dantas, Mario R. Senger, Cleber C. Melo-Filho, Walter C. G. Valente, Ana C. M. de Almeida, João M. Rezende-Neto, Elid F. C. Lima, Ross Paveley, Nicholas Furnham, Eugene Muratov, Lee Kamentsky, Anne E. Carpenter, Rodolpho C. Braga, Floriano P. Silva-Junior, and Carolina Horta Andrade [Universidade Federal de Goiás]

Jou. Med. Chem., **59**, 7075–7088, 2016.

Schistosomiasis is a debilitating neglected tropical disease, caused by flatworms of *Schistosoma* genus. The treatment relies on a single drug, praziquantel (PZQ), making the discovery of new compounds extremely urgent. In this work, we integrated QSAR-based virtual screening (VS) of *Schistosoma mansoni* thioredoxin glutathione reductase (SmTGR) inhibitors and high content screening (HCS) aiming to discover new antischistosomal agents. Initially, binary QSAR models for inhibition of SmTGR were developed and validated using the Organization for Economic Co-operation and Development (OECD) guidance.

Discovery and Structure-Based Optimization of 2-Ureidothiophene-3-carboxylic Acids as Dual Bacterial RNA Polymerase and Viral Reverse Transcriptase Inhibitors

Walid A. M. Elgaher, Kamal K. Sharma, Jörg Haupenthal, Francesco Saladini, Manuel Pires, Eleonore Real, Yves Mély, and Rolf W. Hartmann [Saarland University]

Jou. Med. Chem., **59**, 7212–7222, 2016.

We are concerned with the development of novel anti-infectives with dual antibacterial and antiretroviral activities for MRSA/HIV-1 co-infection. To achieve this goal, we exploited for the first time the mechanistic function similarity between the bacterial RNA polymerase (RNAP) “switch region” and the viral non-nucleoside reverse transcriptase inhibitor (NNRTI) binding site. Starting from our previously discovered RNAP inhibitors, we managed to develop potent RT inhibitors effective against several resistant HIV-1 strains with maintained or enhanced RNAP inhibitory properties following a structure-based design approach.



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Dr. David Busath edited volumes 7-14

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Medicinal Chemistry and Drug Design (Cont'd)

Molecular dynamics at the receptor level of immunodominant myelin oligodendrocyte glycoprotein 35–55 epitope implicated in multiple sclerosis

Mary Patricia Yannakakis, Haralambos Tzoupis, Elena Michailidou, Efthimia Mantzourani, Carmen Simal, Theodore Tselios [University of Patras]

J. Mol.Graph. and Mod., **68**, 78-86, 2016.

Multiple Sclerosis (MS) is a common autoimmune disease whereby myelin is destroyed by the immune system. The disease is triggered by the stimulation of encephalitogenic T-cells via the formation of a trimolecular complex between the Human Leukocyte Antigen (HLA), an immunodominant epitope of myelin proteins and T-cell Receptor (TCR). In this report, Molecular Dynamics (MD) simulations were used to explore the interactions of MOG_{35–55} at the receptor level. A detailed mapping of the developed interactions during the creation of the trimolecular complex is reported.

Identification of phenoxyacetamide derivatives as novel DOT1L inhibitors via docking screening and molecular dynamics simulation

Minghao Luo, Hui Wang, Yi Zou, Shengping Zhang, Jianhu Xiao, Guangde Jiang, Yihua Zhang, Yisheng Lai [Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases]

J. Mol.Graph. and Mod., **68**, 128-139, 2016.

Dot1-like protein (DOT1L) is a histone methyltransferase that has become a novel and promising target for acute leukemias bearing mixed lineage leukemia (MLL) gene rearrangements. In this study, a hierarchical docking-based virtual screening combined with molecular dynamic (MD) simulation was performed to identify DOT1L inhibitors with novel scaffolds. Consequently, 8 top-ranked hits were eventually identified and were further subjected to MD simulation.

Pharmacophore development and screening for discovery of potential inhibitors of ADAMTS-4 for osteoarthritis therapy

Priyanka Verma, Krishna Dalal, Madhu Chopra [Dr. B. R. Ambedkar Center for Biomedical Research]

J. Mol.Mod., **22**, 178, 2016.

In the development of osteoarthritis, aggrecan degrades prior to cartilage destruction. Aggrecanase-1 (ADAMTS-4) is considered to be the major enzyme responsible for cleaving the Glu373–Ala374 bond in the interglobular domain of aggrecan in humans. Therefore, inhibitors of ADAMTS-4 have therapeutic potential in the treatment of osteoarthritis. In the present work, we developed a chemical feature based pharmacophore model of ADAMTS-4 inhibitors using the HipHop module within the Catalyst program package in order to elucidate the structure–activity relationship and to carry out in-silico screening.

Homology modeling, substrate docking, and molecular simulation studies of mycobacteriophage Che12 lysin A

Shainaba A Saadhali, Sameer Hassan, Luke Elizabeth Hanna, Uma Devi Ranganathan, Vanaja Kumar [National Institute for Research in Tuberculosis]

J. Mol.Mod., **22**, 180, 2016.

Mycobacteriophages produce lysins that break down the host cell wall at the end of lytic cycle to release their progenies. The ability to lyse mycobacterial cells makes the lysins significant. Mycobacteriophage Che12 is the first reported temperate phage capable of infecting and lysogenising *Mycobacterium tuberculosis*. Gp11 of Che12 was found to have Chitinase domain that serves as endolysin (lysin A) for Che12. Structure of gp11 was modeled and evaluated using Ramachandran plot in which 98 % of the residues are in the favored and allowed regions.

Medicinal Chemistry and Drug Design (Cont'd)

In-silico studies on DegP protein of Plasmodium falciparum in search of anti-malarials

Drista Sharma, Rani Soni, Sachin Patel, Deepti Joshi, Tarun Kumar Bhatt [Central University of Rajasthan]

J. Mol.Mod., **22**, 201, 2016.

Despite encouraging progress over the past decade, malaria caused by the Plasmodium parasite continues to pose an enormous disease burden and is one of the major global health problems. DegP protein, secretory in nature has been shown to be involved in regulation of thermo-oxidative stress generated during asexual life cycle of Plasmodium, probably required for survival of parasite in host. Considering the significance of protein, in this study, we have generated a three-dimensional structure of PfDegP followed by validation of the modeled structure using several tools like RAMPAGE, ERRAT, and others.

What's My Substrate? Computational Function Assignment of Candida parapsilosis ADH5 by Genome Database Search, Virtual Screening, and QM/MM Calculations

Gaurao V. Dhoke, Yunus Ensari, Mehdi D. Davari, Anna Joëlle Ruff, Ulrich Schwaneberg, and Marco Bocola [RWTH Aachen University]

J.Chem. Infor. and Mod., **56**, 1313–1323, 2016.

Zinc-dependent medium chain reductase from Candida parapsilosis can be used in the reduction of carbonyl compounds to pharmacologically important chiral secondary alcohols. To date, the nomenclature of cpADH5 is differing (CPCR2/RCR/SADH) in the literature, and its natural substrate is not known. In this study, we utilized a substrate docking based virtual screening method combined with KEGG, MetaCyc pathway, and Candida genome databases search for the discovery of natural substrates of cpADH5.

Anti-arrhythmic Medication Propafenone a Potential Drug for Alzheimer's Disease Inhibiting Aggregation of A β : In Silico and in Vitro Studies

Son Tung Ngo, Shang-Ting Fang, Shu-Hsiang Huang, Chao-Liang Chou, Pham Dinh Quoc Huy, Mai Suan Li, and Yi-Cheng Chen [MacKay Medical College, New Taipei City]

J.Chem. Infor. and Mod., **56**, 1344–1356, 2016.

Alzheimer's disease (AD) is the most common form of dementia caused by the formation of A β aggregates. So far, no effective medicine for the treatment of AD is available. Many efforts have been made to find effective medicine to cope with AD. Curcumin is a drug candidate for AD, being a potent anti-amyloidogenic compound, but the results of clinical trials for it were either negative or inclusive. In the present study, we took advantages from accumulated knowledge about curcumin and have screened out four compounds that have chemical and structural similarity with curcumin more than 80% from all FDA-approved oral drugs.

Drug search for leishmaniasis: a virtual screening approach by grid computing

Rodrigo Ochoa, Stanley J. Watowich, Andrés Flórez, Carol V. Mesa, Sara M. Robledo, Carlos Muskus [Universidad de Antioquia]

J.Comp.Aided. Mol.des. **30**, 541-552, 2016.

The trypanosomatid protozoa Leishmania is endemic in ~100 countries, with infections causing ~2 million new cases of leishmaniasis annually. Disease symptoms can include severe skin and mucosal ulcers, fever, anemia, splenomegaly, and death. Unfortunately, therapeutics approved to treat leishmaniasis are associated with potentially severe side effects, including death. Furthermore, drug-resistant Leishmania parasites have developed in most endemic countries. To address an urgent need for new, safe and inexpensive anti-leishmanial drugs, we utilized the IBM World Community Grid to complete computer-based drug discovery screens using unique leishmanial proteins and a database of 600,000 drug-like small molecules.

Quantitative Structure-Activity Relations

Amino substituted benzimidazo[1,2-a]quinolines: Antiproliferative potency, 3D QSAR study and DNA binding properties

Nataša Perin, Raja Nhili, Maja Cindrić, Branimir Bertoša, Darko Vušak, Irena Martin-Kleiner, William Laine, Grace Karminski-Zamola, Marijeta Kralj, Marie-Hélène David-Cordonnier, Marijana Hranjec [University of Zagreb]

Eur Jou Med Chem., **122**, 530-545, 2016.

We describe the synthesis, 3D-derived quantitative structure-activity relationship (QSAR), antiproliferative activity and DNA binding properties of a series of 2-amino, 5-amino and 2,5-diamino substituted benzimidazo[1,2-a]quinolines prepared by environmentally friendly uncatalyzed microwave assisted amination. The antiproliferative activities were assessed in vitro against colon, lung and breast carcinoma cell lines; activities ranged from submicromolar to micromolar. The strongest antiproliferative activity was demonstrated by 2-amino-substituted analogues, whereas 5-amino and or 2,5-diamino substituted derivatives resulted in much less activity.

QSAR-Driven Discovery of Novel Chemical Scaffolds Active against *Schistosoma mansoni*

Cleber C. Melo-Filho, Rafael F. Dantas, Rodolpho C. Braga, Bruno J. Neves, Mario R. Senger, Walter C. G. Valente, João M. Rezende-Neto, Willian T. Chaves, Eugene N. Muratov, Ross A. Paveley, Nicholas Furnham, Lee Kamentsky, Anne E. Carpenter, Floriano P. Silva-Junior, and Carolina H. Andrade [Federal University of Goias]

J.Chem. Infor. and Mod., **56**, 1357–1372, 2016.

Schistosomiasis is a neglected tropical disease that affects millions of people worldwide. Thioredoxin glutathione reductase of *Schistosoma mansoni* (SmTGR) is a validated drug target that plays a crucial role in the redox homeostasis of the parasite. We report the discovery of new chemical scaffolds against *S. mansoni* using a combi-QSAR approach followed by virtual screening of a commercial database and confirmation of top ranking compounds by in vitro experimental evaluation with automated imaging of schistosomula and adult worms.

Carbon Nanoparticles

Molecular dynamics simulation of doxorubicin adsorption on a bundle of functionalized CNT

Akram Izadyar, Nafiseh Farhadian [Ferdowsi University of Mashhad] & Naser Chenarani

J. Biomol. Stru. and Dyn., **34**, 1797-1805, 2016.

In this study, molecular dynamics simulation is used to investigate the adsorption of an anticancer drug, doxorubicin, on bundles of functionalized single-walled carbon nanotubes (SWNTs) in an aqueous solution. Carboxylic group has been selected as the functional group. Molecular dynamics (MD) simulations are performed for both separated systems containing a SWNT bundle and a functionalized carbon nanotube bundle, and results are compared with existing experimental data. MD results show that doxorubicin can be adsorbed on CNTs using different methods such as entrapment within CNT bundle, attachment to the side wall of the CNT, and adsorption on the CNT inner cavity.

Carbon Nanoparticles (Cont'd)

Segmentation and additive approach: A reliable technique to study noncovalent interactions of large molecules at the surface of single-wall carbon nanotubes

Ana M. Torres, Steve Scheiner, Ajit K. Roy, Andrés M. Garay-Tapia, John Bustamante and Tapas Kar [Utah State University, Logan]

J. Comp. Chem., **37**, 1953–1961, 2016.

This investigation explores a new protocol, named Segmentation and Additive approach (SAA), to study exohedral noncovalent functionalization of single-walled carbon nanotubes with large molecules, such as polymers and biomolecules, by segmenting the entire system into smaller units to reduce computational cost. A key criterion of the segmentation process is the preservation of the molecular structure responsible for stabilization of the entire system in smaller segments. Noncovalent interaction of linoleic acid (LA, C₁₈H₃₂O₂), a fatty acid, at the surface of a (10,0) zigzag nanotube is considered for test purposes.

Effect of electric charging on the velocity of water flow in CNT

Hossein Reza Abbasi, S. M. Hossein Karimian [Amirkabir University of Technology (Tehran Polytechnic)]

J. Mol.Mod., **22**, 198, 2016.

The role of electrical charge in controlling the velocity of water molecules in a finite single-walled carbon nanotube (CNT) was studied in detail using molecular dynamics simulation. Different test cases were examined to determine the parameters affecting the control of water-flow velocity in CNT upon electrically charging the surface of a CNT. The results showed that charge magnitude and volume, as well as the charging scenario, are the parameters having greatest effect. The implementation of electric charge on the surface of a CNT was demonstrated to decrease the resistance of CNT to incoming water flow at the entrance, but to increase friction-type resistance to flow along the CNT.

1.2. Biopolymers

Bioinformatics and Cheminformatics

PANTHER-PSEP: predicting disease-causing genetic variants using position-specific evolutionary preservation

Haiming Tang and Paul D. Thomas [University of Southern California, Los Angeles]

Bioinformatics. **32**, 2230-2232, 2016.

PANTHER-PSEP is a new software tool for predicting non-synonymous genetic variants that may play a causal role in human disease. Several previous variant pathogenicity prediction methods have been proposed that quantify evolutionary conservation among homologous proteins from different organisms. PANTHER-PSEP employs a related but distinct metric based on 'evolutionary preservation': homologous proteins are used to reconstruct the likely sequences of ancestral proteins at nodes in a phylogenetic tree, and the history of each amino acid can be traced back in time from its current state to estimate how long that state has been preserved in its ancestors.

Bioinformatics and Cheminformatics (Cont'd)

AlgoRun: a Docker-based packaging system for platform-agnostic implemented algorithms

Abdelrahman Hosny, Paola Vera-Licona, Reinhard Laubenbacher [Jackson Laboratory for Genomic Medicine, CT], and Thibault Favre

Bioinformatics. **32**, 2396-2398, 2016.

There is a growing need in bioinformatics for easy-to-use software implementations of algorithms that are usable across platforms. At the same time, reproducibility of computational results is critical and often a challenge due to source code changes over time and dependencies. The approach introduced in this paper addresses both of these needs with AlgoRun, a dedicated packaging system for implemented algorithms, using Docker technology. Implemented algorithms, packaged with AlgoRun, can be executed through a user-friendly interface directly from a web browser or via a standardized RESTful web API to allow easy integration into more complex workflows.

Protein Secondary Structure

Molecular cloning and in silico characterization of knottin peptide, U2-SCRTX-Lit2, from brown spider (*Loxosceles intermedia*) venom glands

Gabriel Otto Meissner, Pedro Túlio de Resende Lara, Luis Paulo Barbour Scott, Antônio Sérgio Kimus Braz, Daniele Chaves-Moreira, Fernando Hitomi Matsubara, Eduardo Mendonça Soares, Dilza Trevisan-Silva, Luiza Helena Gremski, Silvio. Sanches Veiga, Olga Meiri Chaim [Federal University of Paraná]

J. Mol.Mod., **22**, 196, 2016.

Inhibitor cystine knots (ICKs) are a family of structural peptides with a large number of cysteine residues that form intramolecular disulfide bonds, resulting in a knot. These peptides are involved in a variety of biological functions including predation and defense, and are found in various species, such as spiders, scorpions, sea anemones, and plants. The *Loxosceles intermedia* venom gland transcriptome identified five groups of ICK peptides that represent more than 50 % of toxin-coding transcripts. Here, we describe the molecular cloning of U2-Sicaritoxin-Lit2 (U2-SCRTX-Lit2), bioinformatic characterization, structure prediction, and molecular dynamic analysis.

Comparative or Homology Modeling

Reactive oxygen species and energy machinery: an integrated dynamic model

Kalyani Korla [University of Hyderabad]

J. Biomol. Stru. and Dyn., **34**, 1625-1640, 2016.

The role of several important reactive oxygen species (ROS) on the Krebs cycle, the electron transport chain (ETC) and the two important shuttles has been modelled. Major part of the ROS is produced during oxygen reduction in the ETC, which has been kinetically simulated, and the changes in the final concentrations of several important metabolites were found. The simulation is based on chemical kinetics equation, and the associated set of differential equations was solved by the ordinary differential equation package in Octave.

Comparative or Homology Modeling (Cont'd)

Structural modeling of HLA-B*1502/peptide/carbamazepine/T-cell receptor complex architecture: implication for the molecular mechanism of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis

Peng Zhou [University of Electronic Science and Technology of China], Shilei Zhang, Yewang Wang, Chao Yang & Jian Huang

J. Biomol. Stru. and Dyn., **34**, 1806-1817, 2016.

Drug-induced adverse reactions are a significant problem in healthcare worldwide and are estimated to cost billions of dollars annually in the United States. A portion of such reactions is observed to strongly associate with certain human leukocyte antigen (HLA) alleles; one of the strongest associations is the HLA-B*1502 protein with carbamazepine (CBZ)-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) – the odds ratio value can even be higher than one thousand. In the current study, we attempt to computationally model the atomic-level structure of the complete HLA-B*1502/peptide/CBZ/T-cell receptor (TCR) complex architecture based on prior knowledge obtained from epidemiological investigations as well as in vitro and in vivo assays.

New insights into the stereochemical requirements of the bradykinin B1 receptor antagonists binding

Cecylia S. Lupala, Patricia Gomez-Gutierrez, Juan J. Perez [Universitat Politecnica de Catalunya]

J. Mol.Graph. and Mod., **68**, 184-196, 2016.

Bradykinin (BK) is a nonapeptide involved in several pathophysiological conditions including among others, septic and haemorrhagic shock, anaphylaxis, arthritis, rhinitis, asthma, inflammatory bowel disease. In the present work we have constructed an atomistic model of the B1 receptor and docked diverse available non-peptide antagonists in order to get a deeper insight into the structure-activity relationships involving binding to this receptor. The model was constructed by homology modeling using the chemokine CXC4 and bovine rhodopsin receptors as template.

The dopamine D₂ receptor dimer and its interaction with homobivalent antagonists: homology modeling, docking and molecular dynamics

Agnieszka A. Kaczor [Medical University of Lublin], Manuela Jörg, Ben Capuano

J. Mol.Mod., **22**, 203, 2016.

In order to apply structure-based drug design techniques to G protein-coupled receptor complexes, it is essential to model their 3D structure and to identify regions that are suitable for selective drug binding. For this purpose, we have developed and tested a multi-component protocol to model the inactive conformation of the dopamine D₂ receptor dimer, suitable for interaction with homobivalent antagonists. Our approach was based on protein-protein docking, applying the Rosetta software to obtain populations of dimers as present in membranes with all the main possible interfaces.

Protein Side Chain Confirmation Prediction

Side chain flexibility and the pore dimensions in the GABA_A receptor

Alexey V. Rossokhin [Russian Academy of Medical Sciences], Boris S. Zhorov

J.Comp.Aided. Mol.des. **30**, 559-567, 2016.

Permeation of ions through open channels and their accessibility to pore-targeting drugs depend on the pore cross-sectional dimensions, which are known only for static X-ray and cryo-EM structures. Here, we have built homology models of the closed, open and desensitized $\alpha_1\beta_2\gamma_2$ GABA_A receptor (GABA_AR). The models are based, respectively, on the X-ray structure of α_3 glycine receptor (α_3 GlyR), cryo-EM structure of α_1 GlyR and X-ray structure of β_3 GABA_AR. We employed Monte Carlo energy minimizations to explore how the pore lumen may increase due to repulsions of flexible side chains from a variable-diameter electroneutral atom (an expanding sphere) pulled through the pore.

Protein Conformational Analysis

Mollack: a web server for the automated creation of conformational ensembles for intrinsically disordered proteins

Zachary Ziegler, Molly Schmidt, Thomas Gurry, Virginia Burger, and Collin M. Stultz [Massachusetts Institute of Technology, Cambridge]

Bioinformatics. **32**, 2545-2547, 2016.

Intrinsically disordered proteins (IDPs) play central roles in many biological processes. Consequently, an accurate description of the disordered state is an important step towards a comprehensive understanding of a number of important biological functions. In this work we describe a new web server, Mollack, for the automated construction of unfolded ensembles that uses both experimental and molecular simulation data to construct models for the unfolded state. An important aspect of the method is that it calculates a quantitative estimate of the uncertainty in the constructed ensemble, thereby providing an objective measure of the quality of the final model.

A critical assessment of hidden markov model sub-optimal sampling strategies applied to the generation of peptide 3D models

A. Lamiable, P. Thevenet and P. Tufféry [Université Paris Diderot]

J. Comp. Chem., **37**, 2006–2016, 2016.

Hidden Markov Model derived structural alphabets are a probabilistic framework in which the complete conformational space of a peptidic chain is described in terms of probability distributions that can be sampled to identify conformations of largest probabilities. Here, we assess how three strategies to sample sub-optimal conformations—Viterbi k-best, forward backtrack and a taboo sampling approach—can lead to the efficient generation of peptide conformations.

Protein Conformational Analysis (Cont'd)

Prediction of three-dimensional structures and structural flexibilities of wild-type and mutant cytochrome P450 1A2 using molecular dynamics simulations

Yurie Watanabe, Shuichi Fukuyoshi, Masahiro Hiratsuka, Noriyuki Yamaotsu, Shuichi Hirono, Ohgi Takahashi, Akifumi Oda [Kanazawa University]

J. Mol. Graph. and Mod., **68**, 48-56, 2016.

In this study, we investigated the effect of genetic polymorphism on the three-dimensional (3D) conformation of cytochrome P450 1A2 (CYP1A2) using molecular dynamics (MD) simulations. CYP1A2, a major drug-metabolizing enzyme among cytochrome P450 enzymes (CYPs), is known to have many variant alleles. The genetic polymorphism of CYP1A2 may cause individual differences in the pharmacokinetics of medicines. By performing 100 ns or longer MD simulations, we investigated the influence of amino acid mutation on the 3D structures and the dynamic properties of proteins.

Effect of Inactivating Mutations on Peptide Conformational Ensembles: The Plant Polypeptide Hormone Systemin

Saikat Dutta Chowdhury, Aditya K. Sarkar, and Ansuman Lahiri [University of Calcutta]

J. Chem. Infor. and Mod., **56**, 1267–1281, 2016.

As part of their basal immune mechanism against insect/herbivore attacks, plants have evolved systemic response mechanisms. Such a systemic wound response in tomato was found to involve an 18 amino acid polypeptide called systemin, the first polypeptide hormone to be discovered in plants. We have studied the conformational ensembles of wild-type systemin along with its 17 variants by carrying out a total of 5.76 μ s of replica-exchange molecular dynamics simulation in an implicit solvent environment.

Coarse-Grained Simulations of Heme Proteins: Validation and Study of Large Conformational Transitions

Claudia L. Ramírez, Ariel Petruk, Mauro Bringas, Dario A. Estrin, Adrian E. Roitberg, Marcelo A. Marti, and Luciana Capece [Univ. de Buenos Aires]

J. Chem. Theor. and Comp., **12**, 3390–3397, 2016.

Heme proteins are ubiquitous in nature and perform many diverse functions in all kingdoms of life. Many of these functions are related to large-scale conformational transitions and allosteric processes. In this work, we present a coarse-grained model of the heme group and thoroughly validate this model in different benchmark examples, which include the monomeric heme proteins myoglobin and neuroglobin and the tetrameric human hemoglobin where we evaluated the method's ability to explore conformational changes (as the formation of hexacoordinated species) and allosteric transitions (as the well-known R $\rightarrow$ T transition).

Localization of Millisecond Dynamics: Dihedral Entropy from Accelerated MD

Anna S. Kamenik, Ursula Kahler, Julian E. Fuchs, and Klaus R. Liedl [University of Innsbruck, Innsbruck]

J. Chem. Theor. and Comp., **12**, 3449–3455, 2016.

Here, we demonstrate a method to capture local dynamics on a time scale 3 orders of magnitude beyond state-of-the-art simulation approaches. We apply accelerated molecular dynamics simulations for conformational sampling and extract reweighted backbone dihedral distributions. Local dynamics are characterized by torsional probabilities, resulting in residue-wise dihedral entropies. Our approach is successfully validated for three different protein systems of increasing size: alanine dipeptide, bovine pancreatic trypsin inhibitor (BPTI), and the major birch pollen allergen Bet v 1a.

Protein Conformational Analysis (Cont'd)

Coarse-grained simulations of proton-dependent conformational changes in lactose permease

Yead Jewel, Prashanta Dutta and Jin Liu [Washington State University]

Proteins: Stru. Fun. & Bioinf., **84**, 1067–1074, 2016.

During lactose/H⁺ symport, the Escherichia coli lactose permease (LacY) undergoes a series of global conformational transitions between inward-facing (open to cytoplasmic side) and outward-facing (open to periplasmic side) states. However, the exact local interactions and molecular mechanisms dictating those large-scale structural changes are not well understood. All-atom molecular dynamics simulations have been performed to investigate the molecular interactions involved in conformational transitions of LacY, but the simulations can only explore early or partial global structural changes because of the computational limits (< 100 ns).

Protein Structure Analysis

Local Protein Structure Refinement via Molecular Dynamics Simulations with locPREFMD

Michael Feig [Michigan State University]

J.Chem. Infor. and Mod., **56**, 1304–1312, 2016.

A method for the local refinement of protein structures that targets improvements in local stereochemistry while preserving the overall fold is presented. The method uses force field-based minimization and sampling via molecular dynamics simulations with a modified force field to bring bonds, angles, and torsion angles into an acceptable range for high-resolution protein structures. The method is implemented in the locPREFMD web server and was tested on computational models submitted to CASP11.

Molecular Dynamics Simulations of Intrinsically Disordered Proteins: On the Accuracy of the TIP4P-D Water Model and the Representativeness of Protein Disorder Models

João Henriques [Lund University] and Marie Skepö

J. Chem. Theor. and Comp., **12**, 3407–3415, 2016.

Here, we first present a follow-up to a previous work by our group on the problematic of molecular dynamics simulations of intrinsically disordered proteins (IDPs) [Henriques et al. *J. Chem. Theory Comput.* 2015, 11, 3420–3431], using the recently developed TIP4P-D water model. When used in conjunction with the standard AMBER ff99SB-ILDN force field and applied to the simulation of Histatin 5, our IDP model, we obtain results which are in excellent agreement with the best performing IDP-suitable force field from the earlier study and with experiment.

Protein Dynamics

Genome-scale prediction of moonlighting proteins using diverse protein association information

Ishita K. Khan and Daisuke Kihara [Purdue University]

Bioinformatics. **32**, 2281-2288, 2016.

Moonlighting proteins (MPs) show multiple cellular functions within a single polypeptide chain. To understand the overall landscape of their functional diversity, it is important to establish a computational method that can identify MPs on a genome scale. Previously, we have systematically characterized MPs using functional and omics-scale information. In this work, we develop a computational prediction model for automatic identification of MPs using a diverse range of protein association information.

TreeDom: a graphical web tool for analysing domain architecture evolution

Christian Haider, Marina Kavic, and Erik L.L. Sonnhammer [Stockholm University]

Bioinformatics. **32**, 2384-2385, 2016.

We present TreeDom, a web tool for graphically analysing the evolutionary history of domains in multi-domain proteins. Individual domains on the same protein chain may have distinct evolutionary histories, which is important to grasp in order to understand protein function. For instance, it may be important to know whether a domain was duplicated recently or long ago, to know the origin of inserted domains, or to know the pattern of domain loss within a protein family. TreeDom uses the Pfam database as the source of domain annotations, and displays these on a sequence tree.

Protein Composition Determines the Effect of Crowding on the Properties of Disordered Proteins

Cayla M. Miller, Young C. Kim, Jeetain Mittal [Lehigh University, Bethlehem]

Biophysical Journal., **111**, 28-37, 2016.

Unlike dilute experimental conditions under which biological molecules are typically characterized, the cell interior is crowded by macromolecules, which affects both the thermodynamics and kinetics of in vivo processes. Although the excluded-volume effects of macromolecular crowding are expected to cause compaction of unfolded and disordered proteins, the extent of this effect is uncertain.

The mechanism by which P250L mutation impairs flavivirus-NS1 dimerization: an investigation based on molecular dynamics simulations

Edson R. A. Oliveira, Ricardo B. de Alencastro, Bruno A. C. Horta [Universidade Federal do Rio de Janeiro]

Euro. Biophysical Journal., **45**, 573-580, 2016.

The flavivirus non-structural protein 1 (NS1) is a conserved glycoprotein with as yet undefined biological function. This protein dimerizes when inside infected cells or associated to cell membranes but also forms lipid-associated hexamers when secreted to the extracellular space. A single amino acid substitution (P250L) is capable of preventing the dimerization of NS1 resulting in lower virulence and slower virus replication. In this work, based on molecular dynamics simulations of the dengue-2 virus NS1 β -ladder monomer as a core model, we found that this mutation can induce several conformational changes that importantly affect critical monomer–monomer interactions.

Protein Dynamics (Cont'd)

Molecular dynamics simulations of the free and inhibitor-bound cruzain systems in aqueous solvent: insights on the inhibition mechanism in acidic pH

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J. Biomol. Stru. and Dyn., **34**, 1969-1978, 2016.

The major cysteine protease of *Trypanosoma cruzi*, cruzain (CRZ), has been described as a therapeutic target for Chagas' disease, which affects millions of people worldwide. Thus, a series of CRZ inhibitors has been studied, including a new competitive inhibitor, Nequimed176 (NEQ176). Nevertheless, the structural and dynamic basis for CRZ inhibition remains unclear. Hoping to contribute to this ever-growing understanding of timescale dynamics in the CRZ inhibition mechanism, we have performed the first study using 100 ns of molecular dynamics (MD) simulations of two CRZ systems in an aqueous solvent under pH 5.5: CRZ in the apo form (ligand free) and CRZ complexed to NEQ176.

Efficient implementation of constant pH molecular dynamics on modern graphics processors

Evan J. Arthur and Charles L. Brooks III [University of Michigan, Ann Arbor]

J. Comp. Chem., **37**, 2171–2180, 2016.

The treatment of pH sensitive ionization states for titratable residues in proteins is often omitted from molecular dynamics (MD) simulations. Here, we present a first implementation of GPU-enabled CPHMD within the CHARMM-OpenMM simulation package interface. Depending on the system size and nonbonded force cutoff parameters, we find speed increases of between one and three orders of magnitude.

Thermodynamic compatibility of actives encapsulated into PEG-PLA nanoparticles: In Silico predictions and experimental verification

Andreas Erlebach, Timm Ott, Christoph Otzen, Stephanie Schubert, Justyna Czaplewska, Ulrich S. Schubert and Marek Sierka [Friedrich Schiller University Jena]

J. Comp. Chem., **37**, 2220–2227, 2016.

Achieving optimal solubility of active substances in polymeric carriers is of fundamental importance for a number of industrial applications, including targeted drug delivery within the growing field of nanomedicine. However, its experimental optimization using a trial-and-error approach is cumbersome and time-consuming. Here, an approach based on molecular dynamics (MD) simulations and the Flory–Huggins theory is proposed for rapid prediction of thermodynamic compatibility between active species and copolymers comprising hydrophilic and hydrophobic segments.

Effects of ligand binding on the mechanical stability of protein GB1 studied by steered molecular dynamics simulation

Ji-Guo Su, Shu-Xin Zhao, Xiao-Feng Wang, Chun-Hua Li, Jing-Yuan Li [Chinese Academy of Science]

J. Mol.Mod., **22**, 188, 2016.

Regulation of the mechanical properties of proteins plays an important role in many biological processes, and sheds light on the design of biomaterials comprised of protein. At present, strategies to regulate protein mechanical stability focus mainly on direct modulation of the force-bearing region of the protein. In this work, the impact of ligand binding on the mechanical stability of GB1 was investigated using steered molecular dynamics simulation, and a mechanism underlying the enhanced protein mechanical stability is proposed.

Protein Dynamics (Cont'd)

Molecular dynamics simulations and structure-based network analysis reveal structural and functional aspects of G-protein coupled receptor dimer interactions

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J.Comp.Aided. Mol.des. **30**, 489-512, 2016.

A significant amount of experimental evidence suggests that G-protein coupled receptors (GPCRs) do not act exclusively as monomers but also form biologically relevant dimers and oligomers. However, the structural determinants, stoichiometry and functional importance of GPCR oligomerization remain topics of intense speculation. In this study we attempted to evaluate the nature and dynamics of GPCR oligomeric interactions. A representative set of GPCR homodimers were studied through Coarse-Grained Molecular Dynamics simulations, combined with interface analysis and concepts from network theory for the construction and analysis of dynamic structural networks.

A computational docking study on the pH dependence of peptide binding to HLA-B27 sub-types differentially associated with ankylosing spondylitis

Onur Serçinoğlu, Gülin Özcan, Zeynep Kutlu Kabaş, Pemra Ozbek [Marmara University]

J.Comp.Aided. Mol.des. **30**, 569-581, 2016.

A single amino acid difference (Asp116His), having a key role in a pathogenesis pathway, distinguishes HLA-B*27:05 and HLA-B*27:09 sub-types as associated and non-associated with ankylosing spondylitis, respectively. In this study, molecular docking simulations were carried out with the aim of comprehending the differences in the binding behavior of both alleles at varying pH conditions. A library of modeled peptides was formed upon single point mutations aiming to address the effect of 20 naturally occurring amino acids at the binding core peptide positions.

Oligomer Formation of Amyloid- β (29–42) from Its Monomers Using the Hamiltonian Replica-Permutation Molecular Dynamics Simulation

Satoru G. Itoh and Hisashi Okumura [Institute for Molecular Science, Okazaki]

J. Phys. Chem. B., **120**, 6555–6561, 2016.

Oligomers of amyloid- β peptides (A β) are formed during the early stage of the amyloidogenesis process and exhibit neurotoxicity. The oligomer formation process of A β and even that of A β fragments are still poorly understood, though understanding of these processes is essential for remedying Alzheimer's disease. In order to better understand the oligomerization process of the C-terminal A β fragment A β (29–42) at the atomic level, we performed the Hamiltonian replica-permutation molecular dynamics simulation with A β (29–42) molecules using the explicit water solvent model.

A β 41 Aggregates More Like A β 40 than Like A β 42: In Silico and in Vitro Study

Hoang Linh Nguyen, Tran Thi Minh Thu, Phan Minh Truong, Pham Dang Lan, Viet Hoang Man, Phuong H. Nguyen, Ly Anh Tu, Yi-Cheng Chen, and Mai Suan Li [Polish Academy of Sciences]

J. Phys. Chem. B., **120**, 7371–7379, 2016.

Formation of intracellular plaques and small oligomeric species of amyloid β (A β) peptides inside neurons is a hallmark of Alzheimer's disease. The most abundant A β species in the brain are A β 1-40 and A β 1-42, which are composed, respectively, of 40 and 42 residues. A β 1-42 differs from A β 1-40 only in two residues, Ile41 and Ala42, yet it shows remarkably faster aggregation and greater neurotoxicity than A β 1-40. Secondary structures of the A β 1-41 monomer, which contribute to aggregation propensity, were studied by all-atom molecular dynamics simulation in an implicit solvent and compared to those of A β 1-40 and A β 1-42.

Protein Dynamics (Cont'd)

Replica exchange molecular dynamics simulation of cross-fibrillation of IAPP and PrP106-126

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Proteins: Stru. Fun. & Bioinf., **84**, 1134–1146, 2016.

Aggregation of proteins into amyloid is the central hallmark of a number of protein diseases. Most studies were carried out on the aggregation between proteins of similar species. However, it was observed that some patients with certain protein disease can easily acquire another unrelated protein disease. In this article, we were motivated by an experimental study of aggregation between amylin (Islet Amyloid Polypeptide, IAPP) and prion₁₀₆₋₁₂₆ (PrP106-126) fragment (JACS, 2013, 135, 13582–9).

Free Energy Calculations

CaFE: a tool for binding affinity prediction using end-point free energy methods

Hui Liu and Tingjun Hou [Zhejiang University, Hangzhou]

Bioinformatics. **32**, 2216–2218, 2016.

Accurate prediction of binding free energy is of particular importance to computational biology and structure-based drug design. Among those methods for binding affinity predictions, the end-point approaches, such as MM/PBSA and LIE, have been widely used because they can achieve a good balance between prediction accuracy and computational cost. Here we present an easy-to-use pipeline tool named Calculation of Free Energy (CaFE) to conduct MM/PBSA and LIE calculations.

Estimating binding free energy of a putative growth factors EGF-VEGF complex – a computational bioanalytical study

Meng-Han Lin, C. Allen Chang & Wolfgang B. Fischer [National Yang-Ming University]

J. Biomol. Stru. and Dyn., **34**, 1717–1724, 2016.

Epidermal growth factor (EGF) and homodimeric vascular endothelial growth factor (VEGF) bind to cell surface receptors. They are responsible for cell growth and angiogenesis, respectively. Docking of the individual proteins as monomeric units using ZDOCK 2.3.2 reveals a partial blocking of the receptor binding site of VEGF by EGF. The receptor binding site of EGF is not affected by VEGF. The calculated binding energy is found to be intermediate between the binding energies calculated for Alzheimer's A β 42 and the barnase/barstar complex.

Bound Flavin–Cytochrome Model of Extracellular Electron Transfer in *Shewanella oneidensis*: Analysis by Free Energy Molecular Dynamics Simulations

Gongyi Hong and Ruth Pachter [Wright-Patterson Air Force Base]

J. Phys. Chem. B., **120**, 5617–5624, 2016.

Flavins are known to enhance extracellular electron transfer (EET) in *Shewanella oneidensis* MR-1 bacteria, which reduce electron acceptors through outer-membrane (OM) cytochromes c. Free-shuttle and bound-redox cofactor mechanisms were proposed to explain this enhancement, but recent electrochemical reports favor a flavin-bound model, proposing two one-electron reductions of flavin, namely, oxidized (Ox) to semiquinone (Sq) and semiquinone to hydroquinone (Hq), at anodic and cathodic conditions, respectively. In this work, to provide a mechanistic understanding of riboflavin (RF) binding at the multiheme OM cytochrome OmcA, we explored binding configurations at hemes 2, 5, 7, and 10.

Ligand Binding/Docking

Binding mechanism of CDK5 with roscovitine derivatives based on molecular dynamics simulations and MM/PBSA methods

Keke Dong, Xuan Wang, Xueyu Yang, Xiaolei Zhu [Nanjing Tech University]

J. Mol. Graph. and Mod., **68**, 57-67, 2016.

Roscovitine derivatives are potent inhibitors of cyclin-dependent kinase 5 (CDK5), but they exhibit different activities, which has not been understood clearly up to now. On the other hand, the task of drug design is difficult because of the fuzzy binding mechanism. In this context, the methods of molecular docking, molecular dynamics (MD) simulation, and binding free energy analysis are applied to investigate and reveal the detailed binding mechanism of four roscovitine derivatives with CDK5. The electrostatic and van der Waals interactions of the four inhibitors with CDK5 are analyzed and discussed.

Integration of Ligand and Structure Based Approaches for CSAR-2014

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J. Chem. Infor. and Mod., **56**, 974–987, 2016.

The prediction of binding poses and affinities is an area of active interest in computer-aided drug design (CADD). Given the documented limitations with either ligand or structure based approaches, we employed an integrated approach and developed a rapid protocol for binding mode and affinity predictions. This workflow was applied to the three protein targets of Community Structure–Activity Resource-2014 (CSAR-2014) exercise: Factor Xa (FXa), Spleen Tyrosine Kinase (SYK), and tRNA (guanine-N(1))-methyltransferase (TrmD).

CSAR 2014: A Benchmark Exercise Using Unpublished Data from Pharma

Heather A. Carlson [University of Michigan], Richard D. Smith, Kelly L. Damm-Ganamet, Jeanne A. Stuckey, Aqeel Ahmed, Maire A. Convery, Donald O. Somers, Michael Kranz, Patricia A. Elkins, Guanglei Cui, Catherine E. Peishoff, Millard H. Lambert, and James B. Dunbar Jr.

J. Chem. Infor. and Mod., **56**, 1063–1077, 2016.

The 2014 CSAR Benchmark Exercise was the last community-wide exercise that was conducted by the group at the University of Michigan, Ann Arbor. For this event, GlaxoSmithKline (GSK) donated unpublished crystal structures and affinity data from in-house projects. Three targets were used: tRNA (m1G37) methyltransferase (TrmD), Spleen Tyrosine Kinase (SYK), and Factor Xa (FXa). A particularly strong feature of the GSK data is its large size, which lends greater statistical significance to comparisons between different methods.

Assessment of Solvated Interaction Energy Function for Ranking Antibody–Antigen Binding Affinities

Traian Sulea, Victor Vivcharuk, Christopher R. Corbeil, Christophe Deprez, and Enrico O. Purisima [National Research Council Canada]

J. Chem. Infor. and Mod., **56**, 1292–1303, 2016.

Affinity modulation of antibodies and antibody fragments of therapeutic value is often required in order to improve their clinical efficacies. Virtual affinity maturation has the potential to quickly focus on the critical hotspot residues without the combinatorial explosion problem of conventional display and library approaches. However, this requires a binding affinity scoring function that is capable of ranking single-point mutations of a starting antibody. We focus here on assessing the solvated interaction energy (SIE) function that was originally developed for and is widely applied to scoring of protein–ligand binding affinities.

Enzyme Catalysis

Prediction and verification of novel peptide targets of protein tyrosine phosphatase 1B

Xun Li, Maja Köhn [European Molecular Biology Laboratory]

Bioorg. and Med. Chem., **24**, 3255-3258, 2016

Phosphotyrosine peptides are useful starting points for inhibitor design and for the search for protein tyrosine phosphatase (PTP) phosphoprotein substrates. To identify novel phosphopeptide substrates of PTP1B, we developed a computational prediction protocol based on a virtual library of protein sequences with known phosphotyrosine sites. To these we applied sequence-based methods, biologically meaningful filters and molecular docking. Five peptides were selected for biochemical testing of their potential as PTP1B substrates.

Computational and synthetic approaches for developing Lavendustin B derivatives as allosteric inhibitors of HIV-1 integrase

Fatima E. Agharbaoui, Ashley C. Hoyte, Stefania Ferro, Rosaria Gitto, Maria Rosa Buemi, James R. Fuchs, Mamuka Kvaratskhelia, Laura De Luca [Università di Messina]

Eur Jou Med Chem., **122**, 673-683, 2016.

Through structure-based virtual screening and subsequent activity assays of selected natural products, Lavendustin B was previously identified as an inhibitor of HIV-1 integrase (IN) interaction with its cognate cellular cofactor, lens epithelium-derived growth factor (LEDGF/p75). In order to improve the inhibitory potency we have employed in silico-based approaches. On the basis of these studies, six analogues of Lavendustine B, containing the benzylamino-hydroxybenzoic scaffold, were selected for synthesis and structure activity-relationship (SAR) studies.

Progesterone 5 β -reductases/iridoid synthases (PRISE): gatekeeper role of highly conserved phenylalanines in substrate preference and trapping is supported by molecular dynamics simulations

Jan Petersen, Harald Lanig, Jennifer Munkert, Peter Bauer, Frieder Müller-Uri & Wolfgang Kreis [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J. Biomol. Stru. and Dyn., **34**, 1667-1680, 2016.

Vein Patterning 1 (VEP1)-encoded progesterone 5 β -reductases/iridoid synthases (PRISE) belong to the short-chain dehydrogenase/reductase superfamily of proteins. They are characterized by a set of highly conserved amino acids in the substrate-binding pocket. All PRISEs are capable of reducing the activated C=C double bond of various enones enantioselectively and therefore have a potential as biocatalysts in bioorganic synthesis. Here, recombinant forms of PRISEs of *Arabidopsis thaliana* and *Digitalis lanata* were modified using site-directed mutagenesis (SDM).

Cloning, expression, and molecular dynamics simulations of a xylosidase obtained from *Thermomyces lanuginosus*

Vashni Gramany, Faez Iqbal Khan, Algasan Govender, Krishna Bisetty, Suren Singh & Kugenthiren Permaul [Durban university of technology]

J. Biomol. Stru. and Dyn., **34**, 1681-1692, 2016.

The aim of this study was to clone, express, and characterize a β -xylosidase (Tlxyn1) from the thermophilic fungus *Thermomyces lanuginosus* SSBP in *Pichia pastoris* GS115 as well as analyze optimal activity and stability using computational and experimental methods. The enzyme was constitutively expressed using the GAP promoter and secreted into the medium due to the alpha-mating factor secretion signal present on the expression vector pBGPI. The 1276 bp gene consists of an open reading frame that does not contain introns. A 12% SDS-PAGE gel revealed a major protein band at an estimated molecular mass of 50 kDa which corresponded to zymogram analysis.

Enzyme Catalysis (Cont'd)

Effects of cadmium on the cuttlefish *Sepia pharaonis*' arginine kinase: unfolding kinetics integrated with computational simulations

Yue-Xiu Si, Jinhyuk Lee, Feng Zhao, Shang-Jun Yin, Yong-Doo Park, Guo-Ying Qian [Zhejiang Wanli University] & Xia-Min Jiang

J. Biomol. Stru. and Dyn., **34**, 1763-1777, 2016.

Arginine kinase is closely associated with adaptation to environmental stresses such as high salinity and heavy metal ion levels in marine invertebrates. In this study, the effects of Cd^{2+} on the cuttlefish *Sepia pharaonis*' arginine kinase (SPAK) were investigated. SPAK was isolated from the muscles of *S. pharaonis* and upon further purification, showed a single band on SDS-PAGE. Molecular dynamics simulations involving SPAK and Cd^{2+} showed that Cd^{2+} partly blocks the entrance of ATP to the active site, and this result is consistent with the experimental results showing Cd^{2+} -induced inactivation of SPAK.

A theoretical study on the characteristics of the intermolecular interactions in the active site of human androsterone sulphotransferase: DFT calculations of NQR and NMR parameters and QTAIM analysis

Elahe K. Astani, Emran Heshmati, Chun-Jung Chen, Nasser L. Hadipour [Tarbiat Modares University]

J. Mol.Graph. and Mod., **68**, 14-22, 2016.

A theoretical study at the level of density functional theory (DFT) was performed to characterize noncovalent intermolecular interactions, especially hydrogen bond interactions, in the active site of enzyme human androsterone sulphotransferase (SULT2A1/ADT). Geometry optimization, interaction energy, ^2H , ^{14}N , and ^{17}O electric field gradient (EFG) tensors, ^1H , ^{13}C , ^{17}O , and ^{15}N chemical shielding (CS) tensors, Natural Bonding Orbital (NBO) analysis, and quantum theory of atoms in molecules (QTAIM) analysis of this active site were investigated.

Explaining the autoinhibition of the SMYD enzyme family: A theoretical study

Nizar A. Al-Shar'i, Soraya M. Alnabulsi [Jordan University of Science and Technology]

J. Mol.Graph. and Mod., **68**, 147-157, 2016.

The SMYD enzymes (SMYD1-5) are lysine methyltransferases that have diverse biological functions including gene expression and regulation of skeletal and cardiac muscle development and function. Recently, they have gained more attention as potential drug targets because of their involvement in cardiovascular diseases and in the progression of different cancer types. In this study we aim to investigate and explain the possibility of the regulatory autoinhibition process of the SMYD enzymes by a thorough computational exploration of their dynamic, energetic, and structural changes by using extended molecular dynamics simulations; normal mode analysis (NMA); and energy correlations.

Perspectives for the structure-based design of acetylcholinesterase reactivators

Rodrigo Ochoa, Carlos A. Rodriguez, Andres F. Zuluaga [Universidad de Antioquia]

J. Mol.Graph. and Mod., **68**, 176-183, 2016.

Rational design of active molecules through structure-based methods has been gaining adepts during the last decades due to the wider availability of protein structures, most of them conjugated with relevant ligands. Acetylcholinesterase (AChE) is a molecular target with a considerable amount of data related to its sequence and 3-dimensional structure. In addition, there are structural insights about the mechanism of action of the natural substrate and drugs used in Alzheimer's disease, organophosphorus compounds, among others. We focused on information regarding the design of ligands aimed to reactivate AChE catalytic activity.

Enzyme Catalysis (Cont'd)

Modeling the protonation states of β -secretase binding pocket by molecular dynamics simulations and docking studies

Dima A. Sabbah, Haizhen A. Zhong [The University of Nebraska at Omaha]

J. Mol.Graph. and Mod., **68**, 206-215, 2016.

β -secretase (BACE1) is an aspartyl protease that processes the β -amyloid peptide in the human brain in patients with Alzheimer's disease. There are two catalytic aspartates (ASP32 and ASP228) in the active domain of BACE1. Although it is believed that the net charge of the Asp dyad is -1 , the exact protonation state still remains a matter of debate. We carried out MD simulations for the four protonation states of BACE1 proteins. We applied Glide docking studies to 21 BACE1 inhibitors against the MD extracted conformations. The dynamic results infer that the protein/ligand complex remains stable during the entire simulation course for HD32D228 model.

Investigating the substrate binding mechanism of sulfotransferase 2A1 based on substrate tunnel analysis: a molecular dynamics simulation study

Li Zhao, Pupu Zhang, Shiyang Long, Linlin Wang, Hanyong Jin, Weiwei Han, Pu Tian [Jilin University]

J. Mol.Mod., **22**, 176, 2016.

Cytosolic sulfotransferases (SULTs) catalyze the transfer of a sulfonate group from the unique cofactor 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to a large number of diverse substrates. In this work, tunnels that facilitate the transport of substrates in the enzyme were studied, with and without bound cofactor, using extensive molecular dynamics simulations. Residues making up tunnels, as well as residues forming bottlenecks to the tunnels, were identified. Conformation analysis of the active-site cap was also performed.

Rapid activity prediction of HIV-1 integrase inhibitors: harnessing docking energetic components for empirical scoring by chemometric and artificial neural network approaches

Patcharapong Thangsunan, Sila Kittiwachana, Puttinan Meepowpan, Nawee Kungwan, Panchika Prangkio, Supa Hannongbua, Nuttee Suree [Chiang Mai University]

J.Comp.Aided. Mol.des. **30**, 471-488, 2016.

Improving performance of scoring functions for drug docking simulations is a challenging task in the modern discovery pipeline. Among various ways to enhance the efficiency of scoring function, tuning of energetic component approach is an attractive option that provides better predictions. We present the first development of rapid and simple tuning models for predicting and scoring inhibitory activity of investigated ligands docked into catalytic core domain structures of HIV-1 integrase (IN) enzyme. We developed the models using all energetic terms obtained from flexible ligand-rigid receptor dockings by AutoDock4, followed by a data analysis using either partial least squares (PLS) or self-organizing maps (SOMs).

Computational study of the inhibitory mechanism of the kinase CDK5 hyperactivity by peptide p5 and derivation of a pharmacophore

A. Cardone [University of Maryland], M. Brady, R. Sriram, H. C. Pant, S. A. Hassan

J.Comp.Aided. Mol.des. **30**, 513-521, 2016.

The hyperactivity of the cyclic dependent kinase 5 (CDK5) induced by the activator protein p25 has been linked to a number of pathologies of the brain. The CDK5-p25 complex has thus emerged as a major therapeutic target for Alzheimer's disease (AD) and other neurodegenerative conditions. Experiments have shown that the peptide p5 reduces the CDK5-p25 activity without affecting the endogenous CDK5-p35 activity, whereas the peptide TFP5, obtained from p5, elicits similar inhibition, crosses the blood-brain barrier, and exhibits behavioral rescue of AD mice models with no toxic side effects.

Enzyme Catalysis (Cont'd)

Conformational Heterogeneity in the Michaelis Complex of Lactate Dehydrogenase: An Analysis of Vibrational Spectroscopy Using Markov and Hidden Markov Models

Xiaoliang Pan and Steven D. Schwartz [University of Arizona]

J. Phys. Chem. B., **120**, 6612–6620, 2016.

Lactate dehydrogenase (LDH) catalyzes the interconversion of pyruvate and lactate. Recent isotope-edited IR spectroscopy suggests that conformational heterogeneity exists within the Michaelis complex of LDH, and this heterogeneity affects the propensity toward the on-enzyme chemical step for each Michaelis substrate. By combining molecular dynamics simulations with Markov and hidden Markov models, we obtained a detailed kinetic network of the substates of the Michaelis complex of LDH.

Improved QM/MM Linear-Interaction Energy Model for Substrate Recognition in Zinc-Containing Metalloenzymes

Williams E. Miranda, Van A. Ngo, Pedro A. Valiente, and Sergei Yu. Noskov [University of Calgary]

J. Phys. Chem. B., **120**, 7824–7835, 2016.

One of the essential challenges in the description of receptor–drug interactions in the presence of various polyvalent cations (such as zinc, magnesium, or iron) is the accurate assessment of the electronic effects due to cofactor binding. Here, we examine the role of the explicit account for electronic effects for a panel of small-molecule inhibitors binding to the zinc-aminopeptidase PfA-M1, an essential target for antimalarial drug development.

Protein-Protein Interactions

FRODOCK 2.0: fast protein–protein docking server

Erney Ramírez-Aportela, José Ramón López-Blanco, and Pablo Chacón [Rocasolano Physical Chemistry Institute C.S.I.C.]

Bioinformatics. **32**, 2386–2388, 2016.

The prediction of protein–protein complexes from the structures of unbound components is a challenging and powerful strategy to decipher the mechanism of many essential biological processes. We present a user-friendly protein–protein docking server based on an improved version of FRODOCK that includes a complementary knowledge-based potential. The web interface provides a very effective tool to explore and select protein–protein models and interactively screen them against experimental distance constraints.

Memdock: an α -helical membrane protein docking algorithm

Naama Hurwitz, Dina Schneidman-Duhovny, and Haim J. Wolfson [Tel Aviv University]

Bioinformatics. **32**, 2444–2450, 2016.

A wide range of fundamental biological processes are mediated by membrane proteins. Despite their large number and importance, less than 1% of all 3D protein structures deposited in the Protein Data Bank are of membrane proteins. This is mainly due to the challenges of crystallizing such proteins or performing NMR spectroscopy analyses. We present a novel algorithm, Memdock, for docking α -helical membrane proteins which takes into consideration the lipid bilayer environment for docking as well as for refining and ranking the docking candidates. We show that our algorithm improves both the docking accuracy and the candidates ranking compared to a standard protein–protein docking algorithm.

Protein-Protein Interactions (Cont'd)

Shape complementarity and hydrogen bond preferences in protein-protein interfaces: implications for antibody modeling and protein-protein docking

Daisuke Kuroda and Jeffrey J. Gray [Johns Hopkins University, Baltimore]

Bioinformatics. **32**, 2451-2456, 2016.

Characterizing protein-protein interfaces and the hydrogen bonds is a first step to better understand proteins' structures and functions toward high-resolution protein design. However, there are few large-scale surveys of hydrogen bonds of interfaces. In addition, previous work of shape complementarity of protein complexes suggested that lower shape complementarity in antibody-antigen interfaces is related to their evolutionary origin. Using 6637 non-redundant protein-protein interfaces, we revealed peculiar features of various protein complex types.

Small molecules that target phosphorylation dependent protein-protein interaction

Nobumoto Watanabe [RIKEN Center for Sustainable Resource Science], Hiroyuki Osada

Bioorg. and Med. Chem., **24**, 3246-3254, 2016

Protein-protein interaction is one of the key events in the signal transduction pathway. The interaction changes the conformations, activities, localization and stabilities of the proteins, and transduces the signal to the next step. Frequently, this interaction occurs upon the protein phosphorylation. In this review, we focused on three examples of phosphorylation dependent protein-protein interaction modules (14-3-3, polo box domain of Plk1 and F-box proteins in SCF ubiquitin ligases) and summarize small molecules that modulate their interaction.

Protein-protein interactions between SWCNT/chitosan/EGF and EGF receptor: a model of drug delivery system

Chompoonut Rungnim, Thanyada Rungrotmongkol [Chulalongkorn University], Nawee Kungwan & Supot Hannongbua

J. Biomol. Stru. and Dyn., **34**, 1919-1929, 2016.

Epidermal growth factor (EGF) was used as the targeting ligand to enhance the specificity of a cancer drug delivery system (DDS) via its specific interaction with the EGF receptor (EGFR) that is overexpressed on the surface of some cancer cells. To investigate the intermolecular interaction and binding affinity between the EGF-conjugated DDS and the EGFR, 50 ns molecular dynamics simulations were performed on the complex of tethered EGFR and EGF linked to single-wall carbon nanotube (SWCNT) through a biopolymer chitosan wrapping the tube outer surface (EGFR·EGF-CS-SWCNT-Drug complex), and compared to the EGFR·EGF complex and free EGFR.

Multi-scale molecular dynamics study of cholera pentamer binding to a GM1-phospholipid membrane

Akshay Sridhar, Amit Kumar, Ashok Kumar Dasmahapatra [Indian Institute of Technology Guwahati]

J. Mol.Graph. and Mod., **68**, 236-251, 2016.

The AB₅ type toxin produced by the *Vibrio cholerae* bacterium is the causative agent of the cholera disease. The cholera toxin (CT) has been shown to bind specifically to GM1 glycolipids on the membrane surface. This binding of CT to the membrane is the initial step in its endocytosis and has been postulated to cause significant disruption to the membrane structure. In this work, we have carried out a combination of coarse-grain and atomistic simulations to study the binding of CT to a membrane modelled as an asymmetrical GM1-DPPC bilayer.

Protein-Protein Interactions (Cont'd)

Conformational Heterogeneity of Unbound Proteins Enhances Recognition in Protein-Protein Encounters

Chiara Pallara, Manuel Rueda, Ruben Abagyan, and Juan Fernández-Recio [Barcelona Supercomputing Center]

J. Chem. Theor. and Comp., **12**, 3236–3249, 2016.

To understand cellular processes at the molecular level we need to improve our knowledge of protein-protein interactions, from a structural, mechanistic, and energetic point of view. Current theoretical studies and computational docking simulations show that protein dynamics plays a key role in protein association and support the need for including protein flexibility in modeling protein interactions. Assuming the conformational selection binding mechanism, in which the unbound state can sample bound conformers, one possible strategy to include flexibility in docking predictions would be the use of conformational ensembles originated from unbound protein structures.

Membrane Proteins and Lipid Peptide Interactions

ProtPOS: a python package for the prediction of protein preferred orientation on a surface

Jimmy C. F. Ngai, Pui-In Mak, and Shirley W. I. Siu [Avenida da Universidade, Taipa]

Bioinformatics. **32**, 2537-2538, 2016.

Atomistic molecular dynamics simulation is a promising technique to investigate the energetics and dynamics in the protein-surface adsorption process which is of high relevance to modern biotechnological applications. To increase the chance of success in simulating the adsorption process, favorable orientations of the protein at the surface must be determined. Here, we present ProtPOS which is a lightweight and easy-to-use python package that can predict low-energy protein orientations on a surface of interest.

Probing the structure and dynamics of caveolin-1 in a caveolae-mimicking asymmetric lipid bilayer model

Hanqi Liu, Linlin Yang, Qiansen Zhang, Lingxue Mao, Hualiang Jiang, Huaiyu Yang [Shanghai Institute of Materia Medica]

Euro. Biophysical Journal., **45**, 511-521, 2016.

Caveolin-1 is the principle membrane protein of caveolae and plays an important role in various cellular processes. The protein contains two helices (H1 and H2) connected by a three-residue break. Although caveolin-1 is assumed to adopt a U-shaped conformation in the transmembrane domain, with both the N-terminus and C-terminus exposed to the cytoplasm, the structure and dynamics of caveolin-1 in membranes are still unclear. We performed six MD simulations to characterize the structure and dynamics of caveolin-1 (residues D82–S136; Cav₁₈₂₋₁₃₆) in a caveolae-mimicking asymmetric lipid bilayer.

Uncoupling the Structure-Activity Relationships of β_2 Adrenergic Receptor Ligands from Membrane Binding

Callum J. Dickson [Novartis Institutes for BioMedical Research], Viktor Hornak, Camilo Velez-Vega, Daniel J. J. McKay, John Reilly, David A. Sandham, Duncan Shaw, Robin A. Fairhurst, Steven J. Charlton, David A. Sykes, Robert A. Pearlstein, and Jose S. Duca

Jou. Med. Chem., **59**, 5780–5789, 2016.

Ligand binding to membrane proteins may be significantly influenced by the interaction of ligands with the membrane. In particular, the microscopic ligand concentration within the membrane surface solvation layer may exceed that in bulk solvent, resulting in overestimation of the intrinsic protein-ligand binding contribution to the apparent/measured affinity. Using published binding data for a set of small molecules with the β_2 adrenergic receptor, we demonstrate that deconvolution of membrane and protein binding contributions allows for improved structure-activity relationship analysis and structure-based drug design.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulations and Kinetic Measurements to Estimate and Predict Protein–Ligand Residence Times

Luca Mollica, Isabelle Theret, Mathias Antoine, Françoise Perron-Sierra, Yves Charton, Jean-Marie Fourquez, Michel Wierzbicki, Jean A. Boutin, Gilles Ferry, Sergio Decherchi, Giovanni Bottegoni, Pierre Ducrot, and Andrea Cavalli [CompuNet, Istituto Italiano di Tecnologia]

Jou. Med. Chem., **59**, 7167–7176, 2016.

Ligand–target residence time is emerging as a key drug discovery parameter because it can reliably predict drug efficacy in vivo. Experimental approaches to binding and unbinding kinetics are nowadays available, but we still lack reliable computational tools for predicting kinetics and residence time. Most attempts have been based on brute-force molecular dynamics (MD) simulations, which are CPU-demanding and not yet particularly accurate. We recently reported a new scaled-MD-based protocol, which showed potential for residence time prediction in drug discovery. Here, we further challenged our procedure's predictive ability by applying our methodology to a series of glucokinase activators that could be useful for treating type 2 diabetes mellitus.

HybridDock: A Hybrid Protein–Ligand Docking Protocol Integrating Protein- and Ligand-Based Approaches

Sheng-You Huang, Min Li, Jianxin Wang [University of Missouri, Columbia], and Yi Pan

J.Chem. Infor. and Mod., **56**, 1078–1087, 2016.

Structure-based molecular docking and ligand-based similarity search are two commonly used computational methods in computer-aided drug design. Structure-based docking tries to utilize the structural information on a drug target like protein, and ligand-based screening takes advantage of the information on known ligands for a target. Here, we have presented a general hybrid docking protocol, referred to as HybridDock, to utilize both the protein structures and known ligands by combining the molecular docking program MDock and the ligand-based similarity search method SHAFTS, and evaluated our hybrid docking protocol on the CSAR 2013 and 2014 exercises.

Combined Approach of Patch-Surfer and PL-PatchSurfer for Protein–Ligand Binding Prediction in CSAR 2013 and 2014

Xiaolei Zhu, Woong-Hee Shin, Hyungrae Kim, and Daisuke Kihara [Purdue University, West Lafayette]

J.Chem. Infor. and Mod., **56**, 1088–1099, 2016.

The Community Structure–Activity Resource (CSAR) benchmark exercise provides a unique opportunity for researchers to objectively evaluate the performance of protein–ligand docking methods. Patch-Surfer and PL-PatchSurfer, molecular surface-based methods for predicting binding ligands of proteins developed in our group, were tested on both CSAR 2013 and 2014 benchmark exercises in combination with an empirical scoring function-based method, AutoDock, while we only participated in CSAR 2013 using Patch-Surfer.

Simulations of Pore Formation in Lipid Membranes: Reaction Coordinates, Convergence, Hysteresis, and Finite-Size Effects

Neha Awasthi and Jochen S. Hub [Georg-August-Universität]

J. Chem. Theor. and Comp., **12**, 3261–3269, 2016.

Transmembrane pores play an important role in various biophysical processes such as membrane permeation, membrane fusion, and antimicrobial peptide activity. In principal, all-atom molecular dynamics (MD) simulations provide an accurate model of pore formation in lipid membranes. In this study, we used umbrella sampling to compute PMFs for pore formation using three different reaction coordinates, namely, (i) a coordinate that steers the lipids in the lateral direction away from the pore center, (ii) the distance of a single lipid phosphate group from the membrane center, and (iii) the average water density inside a membrane-spanning cylinder.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Properties of Poloxamer Molecules and Poloxamer Micelles Dissolved in Water and Next to Lipid Bilayers: Results from Computer Simulations

Upendra Adhikari, Ardeshtir Goliaei, Levan Tsereteli, and Max L. Berkowitz [University of North Carolina at Chapel Hill]

J. Phys. Chem. B., **120**, 5823–5830, 2016.

To study the properties of poloxamer molecules P85 and P188 and micelles containing these poloxamers in bulk water and also next to lipid bilayers, we performed coarse-grained molecular dynamics computer simulations. We used MARTINI force-field and adjusted Lennard-Jones nonbonded interaction strength parameters for poloxamer beads to take into account the presence of polarizable water. Simulations of systems containing poloxamer molecules or micelles solvated in bulk water showed that structural properties, such as radii of gyration of the molecules and micelles, agree with the ones inferred from experiments.

Effect of Saturated Very Long-Chain Fatty Acids on the Organization of Lipid Membranes: A Study Combining ^2H NMR Spectroscopy and Molecular Dynamics Simulations

Adrian Paz Ramos, Patrick Lagüe, Guillaume Lamoureux, and Michel Lafleur [Université de Montréal]

J. Phys. Chem. B., **120**, 6951–6960, 2016.

Little is known about the interaction of very long-chain saturated fatty acids (VLCFAs) with biological membranes. However, this could play an important role on interleaflet interactions and signal transduction mechanisms in cells. The aim of this work is to determine how VLCFA structurally adapts in fluid phospholipid bilayers, since both species must exhibit a significant hydrophobic mismatch. The membrane organization has been described by means of ^2H NMR and molecular dynamics simulations.

Protein Folding

Structured and Unstructured Binding of an Intrinsically Disordered Protein as Revealed by Atomistic Simulations

Raúl Esteban Ithuralde, Adrián Enrique Roitberg, and Adrián Gustavo Turjanski [Ciudad Universitaria]

J. Am. Chem. Soc., **138**, 8742–8751, 2016.

Intrinsically disordered proteins (IDPs) are a set of proteins that lack a definite secondary structure in solution. IDPs can acquire tertiary structure when bound to their partners; therefore, the recognition process must also involve protein folding. The nature of the transition state (TS), structured or unstructured, determines the binding mechanism. The characterization of the TS has become a challenge for experimental techniques and molecular simulations since diffusion, and binding is coupled to folding. We present atomistic MD simulations that sample the free energy surface of the coupled folding and binding of the transcription factor c-myc to the cotranscription factor CREB binding protein (CBP).

Simulation of coupled folding and binding of an intrinsically disordered protein in explicit solvent with metadynamics

Mengzhi Han, Ji Xu, Ying Ren [Chinese Academy of Sciences, Jinghai Li]

J. Mol. Graph. and Mod., **68**, 114–127, 2016.

The C-terminal domain of measles virus nucleoprotein is an intrinsically disordered protein that could bind to the X domain (XD) of phosphoprotein P to exert its physiological function. Experiments reveal that the minimal binding unit is a 21-residue α -helical molecular recognition element (α -MoRE-MeV), which adopts a fully helical conformation upon binding to XD. In this work, two advanced sampling methods, metadynamics and parallel tempering, are combined to characterize the free energy surface of this process and investigate the underlying mechanism.

Protein Folding (Cont'd)

NTL9 Folding at Constant pH: The Importance of Electrostatic Interaction and pH Dependence

Vinícius G. Contessoto, Vinícius M. de Oliveira, Sidney J. de Carvalho, Leandro C. Oliveira, and Vitor B. P. Leite [Universidade Estadual Paulista (UNESP)]

J. Chem. Theor. and Comp., **12**, 3270–3277, 2016.

The folding process of the N-terminal domain of ribosomal protein L9 (NTL9) was investigated at constant-pH computer simulations. Evaluation of the role of electrostatic interaction during folding was carried out by including a Debye–Hückel potential into a C_α structure-based model (SBM). In this study, the charges of the ionizable residues and the electrostatic potential are susceptible to the solution conditions, such as pH and ionic strength, as well as to the presence of charged groups.

Accurate Estimation of Protein Folding and Unfolding Times: Beyond Markov State Models

Ernesto Suárez, Joshua L. Adelman, and Daniel M. Zuckerman [University of Pittsburgh, Pittsburgh]

J. Chem. Theor. and Comp., **12**, 3473–3481, 2016.

Because standard molecular dynamics (MD) simulations are unable to access time scales of interest in complex biomolecular systems, it is common to “stitch together” information from multiple shorter trajectories using approximate Markov state model (MSM) analysis. However, MSMs may require significant tuning and can yield biased results. Here, by analyzing some of the longest protein MD data sets available (>100 μ s per protein), we show that estimators constructed based on exact non-Markovian (NM) principles can yield significantly improved mean first-passage times (MFPTs) for protein folding and unfolding.

Protein-Nucleic acid Interactions

gkmSVM: an R package for gapped-kmer SVM

Mahmoud Ghandi, Morteza Mohammad-Noori, Narges Ghareghani, Dongwon Lee, Levi Garraway, and Michael A. Beer [Johns Hopkins University]

Bioinformatics. **32**, 2205–2207, 2016.

We present a new R package for training gapped-kmer SVM classifiers for DNA and protein sequences. We describe an improved algorithm for kernel matrix calculation that speeds run time by about 2 to 5-fold over our original gkmSVM algorithm. gkmSVM package is freely available through the Comprehensive R Archive Network (CRAN), for Linux, Mac OS and Windows platforms. The C++ implementation is available at www.beerlab.org/gkmsvm.

Dynamic Coupling among Protein Binding, Sliding, and DNA Bending Revealed by Molecular Dynamics

Cheng Tan, Tsuyoshi Terakawa, and Shoji Takada [Kyoto University]

J. Am. Chem. Soc., **138**, 8512–8522, 2016.

Protein binding to DNA changes the DNA's structure, and altered DNA structure can, in turn, modulate the dynamics of protein binding. This mutual dependency is poorly understood. Here we investigated dynamic couplings among protein binding to DNA, protein sliding on DNA, and DNA bending by applying a coarse-grained simulation method to the bacterial architectural protein HU and 14 other DNA-binding proteins. First, we verified our method by showing that the simulated HU exhibits a weak preference for A/T-rich regions of DNA and a much higher affinity for gapped and nicked DNA, consistent with biochemical experiments.

Protein - Nucleic Acid Interactions (Cont'd)

Monte Carlo Tightly Bound Ion Model: Predicting Ion-Binding Properties of RNA with Ion Correlations and Fluctuations

Li-Zhen Sun and Shi-Jie Chen [University of Missouri, Columbia]

J. Chem. Theor. and Comp, **12**, 3370–3381, 2016.

Experiments have suggested that ion correlation and fluctuation effects can be potentially important for multivalent ions in RNA folding. However, most existing computational methods for the ion electrostatics in RNA folding tend to ignore these effects. The previously reported tightly bound ion (TBI) model can treat ion correlation and fluctuation but its applicability to biologically important RNAs is severely limited by the low computational efficiency. Here, on the basis of Monte Carlo sampling for the many-body ion distribution, we develop a new computational model, the Monte Carlo tightly bound ion (MCTBI) model, for ion-binding properties around an RNA.

Divalent Ion Dependent Conformational Changes in an RNA Stem-Loop Observed by Molecular Dynamics

Christina Bergonzo, Kathleen B. Hall, and Thomas E. Cheatham III [University of Utah, Salt Lake City]

J. Chem. Theor. and Comp, **12**, 3382–3389, 2016.

We compare the performance of five magnesium (Mg^{2+}) ion models in simulations of an RNA stem loop which has an experimentally determined divalent ion dependent conformational shift. We show that despite their differences in parametrization and resulting van der Waals terms, including differences in the functional form of the nonbonded potential, when the RNA adopts its folded conformation, all models behave similarly across ten independent microsecond length simulations with each ion model.

Role of Static and Dynamic Obstacles in the Protein Search for Targets on DNA

Alexey Shvets, Maria Kochugaeva, and Anatoly B. Kolomeisky [Rice University, Houston]

J. Phys. Chem. B., **120**, 5802–5809, 2016.

Protein search for specific sequences on DNA marks the beginning of major biological processes. Experiments indicate that proteins find and recognize their targets quickly and efficiently. Because of the large number of experimental and theoretical investigations, there is a reasonable understanding of the protein search processes in purified in vitro systems. However, the situation is much more complex in live cells where multiple biochemical and biophysical processes can interfere with the protein search dynamics. In this study, we develop a theoretical method that explores the effect of crowding on DNA chains during the protein search.

DNA Scrunching in the Packaging of Viral Genomes

James T. Waters, Harold D. Kim, James C. Gumbart, Xiang-Jun Lu, and Stephen C. Harvey [University of Pennsylvania, Philadelphia]

J. Phys. Chem. B., **120**, 6200–6207, 2016.

The motors that drive double-stranded DNA (dsDNA) genomes into viral capsids are among the strongest of all biological motors for which forces have been measured, but it is not known how they generate force. We previously proposed that the DNA is not a passive substrate but that it plays an active role in force generation. In this study, we examined the interactions of dsDNA with the dodecameric connector protein of bacteriophage $\phi 29$, using molecular dynamics simulations on four different DNA sequences, starting from two different conformations (A-DNA and B-DNA).

Protein - Nucleic Acid Interactions (Cont'd)

Atomic-Scale Molecular Dynamics Simulations of DNA–Polycation Complexes: Two Distinct Binding Patterns

Diana A. Kondinskaia, Andrei Yu. Kostritskii, Alexey M. Nesterenko, Alexandra Yu. Antipina, and Andrey A. Gurtovenko [St. Petersburg State University]

J. Phys. Chem. B., **120**, 6546–6554, 2016.

Synthetic cationic polymers represent a promising class of delivery vectors for gene therapy. Here, we employ atomistic molecular dynamics simulations to gain insight into the structure and properties of complexes of DNA with four linear polycations: polyethylenimine (PEI), poly-l-lysine (PLL), polyvinylamine (PVA), and polyallylamine (PAA). These polycations differ in their polymer geometries, protonation states, and hydrophobicities of their backbone chains. Overall, our results demonstrate for the first time the existence of two distinct patterns of binding of DNA with polycations.

Nucleic Acids

e23D: database and visualization of A-to-I RNA editing sites mapped to 3D protein structures

Oz Solomon [Sheba Medical Center, Ramat-Gan], Eran Eyal, Ninette Amariglio, Ron Unger, and Gidi Rechavi

Bioinformatics. **32**, 2213–2215, 2016.

e23D, a database of A-to-I RNA editing sites from human, mouse and fly mapped to evolutionary related protein 3D structures, is presented. Genomic coordinates of A-to-I RNA editing sites are converted to protein coordinates and mapped onto 3D structures from PDB or theoretical models from ModBase. e23D allows visualization of the protein structure, modeling of recoding events and orientation of the editing with respect to nearby genomic functional sites from databases of disease causing mutations and genomic polymorphism.

Anisotropy of B-DNA Groove Bending

Ning Ma and Arjan van der Vaart [University of South Florida]

J. Am. Chem. Soc., **138**, 9951–9958, 2016.

DNA bending is critical for DNA packaging, recognition, and repair, and occurs toward either the major or the minor groove. The anisotropy of B-DNA groove bending was quantified for eight DNA sequences by free energy simulations employing a novel reaction coordinate. The simulations show that bending toward the major groove is preferred for non-A-tracts while the A-tract has a high tendency of bending toward the minor groove. Persistence lengths were generally larger for bending toward the minor groove, which is thought to originate from differences in groove hydration.

Molecular Dynamics Simulation Study of Parallel Telomeric DNA Quadruplexes at Different Ionic Strengths: Evaluation of Water and Ion Models

Matúš Rebič, Aatto Laaksonen, Jiří Šponer, Jozef Uličný, and Francesca Mocci [Arrhenius Laboratory, Stockholm University]

J. Phys. Chem. B., **120**, 7380–7391, 2016.

Most molecular dynamics (MD) simulations of DNA quadruplexes have been performed under minimal salt conditions using the Åqvist potential parameters for the cation with the TIP3P water model. Recently, this combination of parameters has been reported to be problematic for the stability of quadruplex DNA, especially caused by the ion interactions inside or near the quadruplex channel. Here, we verify how the choice of ion parameters and water model can affect the quadruplex structural stability and the interactions with the ions outside the channel.

Nucleic Acids (Cont'd)

Effects of Concentration and Temperature on DNA Hybridization by Two Closely Related Sequences via Large-Scale Coarse-Grained Simulations

Cade B. Markegard, Cameron P. Gallivan, Darrell D. Cheng, and Hung D. Nguyen [University of California, Irvine]

J. Phys. Chem. B., **120**, 7795–7806, 2016.

A newly developed coarse-grained model called BioModi is utilized to elucidate the effects of temperature and concentration on DNA hybridization in self-assembly. Large-scale simulations demonstrate that complementary strands of either the tetrablock sequence or randomized sequence with equivalent number of cytosine or guanine nucleotides can form completely hybridized double helices. Even though the end states are the same for the two sequences, there exist multiple kinetic pathways that are populated with a wider range of transient aggregates of different sizes in the system of random sequences compared to that of the tetrablock sequence.

Surfaces, Catalysts, and Materials Subjects

Peptides design based on transmembrane Escherichia coli's OmpA protein through molecular dynamics simulations in water–dodecane interfaces

Sonia M. Aguilera-Segura, Vanessa Núñez Vélez, Luke Achenie, Oscar Álvarez Solano, Rodrigo Torres, Andrés Fernando González Barrios [Universidad de los Andes]

J. Mol. Graph. and Mod., **68**, 216–223, 2016.

Recent research efforts have focused on the production of environmentally nonthreatening products, including identifying biosurfactants that can replace conventional surfactants. In order to utilize biosurfactants in different industries such as cosmetic, food or petroleum, it is necessary to understand the underpinnings behind the interactions that could take place for biosurfactants which display potential for interface activity. This work aimed to use molecular dynamics simulations to understand the interactions of rationally obtained peptide sequences from the original sequence of the OmpA gene in Escherichia coli, based on the free energy change (ΔG) during peptide insertion at the water–dodecane interface.

Toward a Standard Protocol for Micelle Simulation

Michael A. Johnston, William C. Swope, Kirk E. Jordan, Patrick B. Warren, Massimo G. Noro, David J. Bray, and Richard L. Anderson [SciTech Daresbury]

J. Phys. Chem. B., **120**, 6337–6351, 2016.

In this paper, we present protocols for simulating micelles using dissipative particle dynamics (and in principle molecular dynamics) that we expect to be appropriate for computing micelle properties for a wide range of surfactant molecules. The protocols address challenges in equilibrating and sampling, specifically when kinetics can be very different with changes in surfactant concentration, and with minor changes in molecular size and structure, even using the same force field parameters. We demonstrate that detection of equilibrium can be automated and is robust, for the molecules in this study and others we have considered.

2. METHODOLOGY

Potentials and Parameters

Examination of the quality of various force fields and solvation models for the equilibrium simulations of GA88 and GB88

Juan Zeng [Peking University Shenzhen Graduate School],
Yongxiu Li, John Z.H. Zhang, Ye Mei

J. Mol.Mod., **22**, 177, 2016.

Elucidating the relationship between sequence and conformation is essential for the understanding of functions of proteins. While sharing 88 % sequence identity and differing by only seven residues, GA88 and GB88 have completely different structures and serve as ideal systems for investigating the relationship between sequence and function. In this work, several AMBER force fields (AMBER03, AMBER99SB, AMBER12SB, AMBER14SB, AMBER96) and solvent models (TIP3P, IGB5, IGB7, IGB8) have been employed in the simulations of GA88 and GB88.

Molecular Dynamics

Characterization of Zebrafish Cardiac and Slow Skeletal Troponin C Paralogs by MD Simulation and ITC

Charles M. Stevens, Kaveh Rayani, Christine E. Genge,
Gurpreet Singh, Bo Liang, Janine M. Roller, Cindy Li,
Alison Yueh Li, D. Peter Tieleman, Filip van Petegem,
Glen F. Tibbits [Simon Fraser University, Burnaby]

Biophysical Journal., **111**, 38-49, 2016.

Zebrafish, as a model for teleost fish, have two paralogous troponin C (TnC) genes that are expressed in the heart differentially in response to temperature acclimation. Upon Ca^{2+} binding, TnC changes conformation and exposes a hydrophobic patch that interacts with troponin I and initiates cardiac muscle contraction. Teleost-specific TnC paralogs have not yet been functionally characterized. In this study we have modeled the structures of the paralogs using molecular dynamics simulations at 18°C and 28°C and calculated the different Ca^{2+} -binding properties between the teleost cardiac (cTnC or TnC1a) and slow-skeletal (ssTnC or TnC1b) paralogs through potential-of-mean-force calculations.

Hydrogen bonds in Zif268 proteins – a theoretical perspective

Umadevi Palanivel & Senthilkumar Lakshmiopathi [Bharathiar University]

J. Biomol. Stru. and Dyn., **34**, 1607-1624, 2016.

The aim of the work was to elucidate the presence of different hydrogen bond (H-bond) in five Zif268 proteins (1A1F, 1A1G, 1A1H, 1A1I and 1A1K). For this purpose, we have performed the QM/MM and molecular dynamics (MD) studies, the results of which reveal that H-bonds depend on the amino acid sequence and orientation of the H-bond donor atoms. Further, high specificity of Arg and Asn is observed for guanine and adenine, respectively. Furthermore, both conventional and non-conventional hydrogen bond also exists in the proteins, among them N–H...O H-bonds are the strongest.

Molecular Dynamics (Cont'd)

In silico designing of hyper-glycosylated analogs for the human coagulation factor IX

Fahimeh Ghasemi, Alireza Zomorodipour, Ali Asghar Karkhane, M.Reza Khorramizadeh [Tehran University of Medical Sciences]

J. Mol.Graph. and Mod., **68**, 39-47, 2016.

N-glycosylation is a process during which a glycan moiety attaches to the asparagine residue in the N-glycosylation consensus sequence (Asn-Xxx-Ser/Thr), where Xxx can be any amino acid except proline. In this work, a computational approach was conducted to select suitable location(s) for introducing new N-glycosylation sites into the human coagulation factor IX (hFIX). With this aim, the first 45 residues of mature hFIX were explored to find out suitable positions for introducing either Asn or Ser/Thr residues, to create new N-glycosylation site(s). Our exploration lead to detection of five potential positions, for hyper-glycosylation.

Using Wavelet Analysis To Assist in Identification of Significant Events in Molecular Dynamics Simulations

Zahra Heidari, Daniel R. Roe, Rodrigo Galindo-Murillo, Jahan B. Ghasemi, and Thomas E. Cheatham III [University of Utah, Salt Lake City]

J.Chem. Infor. and Mod., **56**, 1282–129, 2016.

Long time scale molecular dynamics (MD) simulations of biological systems are becoming increasingly commonplace due to the availability of both large-scale computational resources and significant advances in the underlying simulation methodologies. Therefore, it is useful to investigate and develop data mining and analysis techniques to quickly and efficiently extract the biologically relevant information from the incredible amount of generated data. Wavelet analysis (WA) is a technique that can quickly reveal significant motions during an MD simulation.

Forced Desorption of Bovine Serum Albumin and Lysozyme from Graphite: Insights from Molecular Dynamics Simulation

Christian Mücksch and Herbert M. Urbassek [Erwin-Schrödinger-Straße]

J. Phys. Chem. B., **120**, 7889–7895, 2016.

We use molecular dynamics (MD) simulation to study the adsorption and desorption of two widely different proteins, bovine serum albumin (BSA) and lysozyme, on a graphite surface. The adsorption is modeled using accelerated MD to allow the proteins to find optimum conformations on the surface. Our results demonstrate that the “hard protein” lysozyme retains much of its secondary structure during adsorption, whereas BSA loses it almost completely. BSA has a considerably larger adsorption energy compared to that of lysozyme, which does not scale with chain length.

Insights into mechanism of pyrido[2,3-d]pyrimidines as DYRK1A inhibitors based on molecular dynamic simulations

Jiao Jiao Li, Yue Li Tian, Hong Lin Zhai [Lanzhou University, Lanzhou], Min Lv and Xiao Yun Zhang

Proteins: Stru. Fun. & Bioinf., **84**, 1108–1123, 2016.

DYRK1A is characterized by the early development and regulation of neuronal proliferation, and its over expression gives rise to neurological abnormalities. As the promising DYRK1A inhibitors, the binding mechanism between DYRK1A and pyrido[2,3-d]pyrimidines derivatives at molecular level are still veiled. In this article, it was achieved to get the structural insights into pyrido[2,3-d]pyrimidines derivatives as DYRK1A inhibitors by means of comprehensive computational approaches involving molecular docking, molecular dynamics simulation, free energy calculation, and energy decomposition analysis.

QM and QM/MM

Three pillars for achieving quantum mechanical molecular dynamics simulations of huge systems: Divide-and-conquer, density-functional tight-binding, and massively parallel computation

Hiroaki Nishizawa, Yoshifumi Nishimura, Masato Kobayashi, Stephan Irle and Hiromi Nakai [Waseda University]

J. Comp. Chem., **37**, 1983–1992, 2016.

The linear-scaling divide-and-conquer (DC) quantum chemical methodology is applied to the density-functional tight-binding (DFTB) theory to develop a massively parallel program that achieves on-the-fly molecular reaction dynamics simulations of huge systems from scratch. The functions to perform large scale geometry optimization and molecular dynamics with DC-DFTB potential energy surface are implemented to the program called DC-DFTB-K. A novel interpolation-based algorithm is developed for parallelizing the determination of the Fermi level in the DC method.

Inverse Ubbelohde effect in the short hydrogen bond of photosystem II: Relation between H/D isotope effect and symmetry in potential energy profile

Yusuke Kanematsu, Masanori Tachikawa and Yu Takano [Hiroshima City University]

J. Comp. Chem., **37**, 2140–2145, 2016.

The short hydrogen bond between tyrosine Y_z and D1-His190 of photosystem II (PSII) was investigated using multicomponent quantum mechanics, where the quantum fluctuation of a hydrogen nucleus was incorporated into electronic structure calculation. Our computation demonstrated that the deuteration for hydrogen in the short hydrogen bond of PSII led to the reduction of the O...N distance. It indicated an inverse Ubbelohde effect typically recognized in strong and symmetric hydrogen-bonding clusters such as FHF⁻ and H₃O₂⁻.

QM/MM investigation of the reaction rates of substrates of 2,3-dimethylmalate lyase: A catabolic protein isolated from *Aspergillus niger*

Warot Chotapatiwetchkul, Nathjanan Jongkon, Supa Hannongbua, M. Paul Gleeson [Kasetsart University]

J. Mol.Graph. and Mod., **68**, 29-38, 2016.

Aspergillus niger is an industrially important microorganism used in the production of citric acid. It is a common cause of food spoilage and represents a health issue for patients with compromised immune systems. In our efforts to better understand this class of protein, we investigate the catalytic mechanism of DMML, studying five different substrates and two different active site metals configurations using molecular dynamics (MD) and hybrid quantum mechanics/molecular mechanics (QM/MM) calculations.

Influence of the chelator structures on the stability of Re and Tc tricarbonyl complexes with iminodiacetic acid tridentate ligands: a computational study

Daniel Hernández-Valdés, Zalua Rodríguez-Riera, Alicia Díaz-García, Eric Benoist, Ulises Jáuregui-Haza [Instituto Superior de Tecnología y Ciencias Aplicadas]

J. Mol.Mod., **22**, 179, 2016.

The development of novel radiopharmaceuticals for nuclear medicine based on M(CO)₃ (M = Tc, Re) complexes has attracted great attention. The versatility of this core and the easy production of the fac-[M(CO)₃(H₂O)₃]⁺ precursor could explain this interest. The main characteristics of these tricarbonyl complexes are the high substitution stability of the three CO ligands and the corresponding lability of the coordinated water molecules, yielding, via easy exchange of a variety of bi- and tridentate ligands, complexes of very high kinetic stability. Here, a computational study of different tricarbonyl complexes of Re(I) and Tc(I) was performed using density functional theory.

QM and QM/MM (Cont'd)

A QM/MM Approach Using the AMOEBA Polarizable Embedding: From Ground State Energies to Electronic Excitations

Daniele Loco, Étienne Polack, Stefano Caprasecca, Louis Lagardère, Filippo Lipparini, Jean-Philip Piquemal, and Benedetta Mennucci [Università di Pisa]

J. Chem. Theor. and Comp., **12**, 3654–3661, 2016.

A fully polarizable implementation of the hybrid quantum mechanics/molecular mechanics approach is presented, where the classical environment is described through the AMOEBA polarizable force field. A variational formalism, offering a self-consistent relaxation of both the MM induced dipoles and the QM electronic density, is used for ground state energies and extended to electronic excitations in the framework of time-dependent density functional theory combined with a state specific response of the classical part.

Ligand Docking

Identification of small-molecule compounds targeting the dishevelled PDZ domain by virtual screening and binding studies

Jiwon Choi, SongLing Ma, Hyun-Yi Kim, Ji-Hye Yun, Jung-Nyoung Heo, Weontae Lee, Kang-Yell Choi, Kyoung Tai No [Bioinformatics and Molecular Design Research Center, Seoul]

Bioorg. and Med. Chem., **24**, 3259-3266, 2016

The Dishevelled (Dvl) protein, which conveys signals from receptors to the downstream effectors, is a critical constituent of the Wnt/ β -catenin signaling pathway. Because the PDZ domain of Dvl protein functions through associations with a wide range of protein partners, Dvl protein involved in the Wnt signaling pathway has been considered to be therapeutic targets in cancers. In this study, we performed structure-based pharmacophore model of the Dvl PDZ domain to discover novel small-molecule binders and identified eight compounds with micromolar affinity.

The Molecular Switching Mechanism at the Conserved D(E)RY Motif in Class-A GPCRs

Angelica Sandoval, Stefanie Eichler, Sineej Madathil, Philip J. Reeves, Karim Fahmy, Rainer A. Böckmann [Friedrich-Alexander Universität Erlangen-Nürnberg]

Biophysical Journal., **111**, 79-89, 2016.

The disruption of ionic and H-bond interactions between the cytosolic ends of transmembrane helices TM3 and TM6 of class-A (rhodopsin-like) G protein-coupled receptors (GPCRs) is a hallmark for their activation by chemical or physical stimuli. In the bovine photoreceptor rhodopsin, this is accompanied by proton uptake at Glu¹³⁴ in the class-conserved D(E)RY motif. However, the molecular details of this linkage could not be resolved and have been addressed in this study by molecular dynamics (MD) simulations on TM3 model peptides in a bilayer of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC).

Capturing state-dependent dynamic events of GABA_A-receptors: a microscopic look into the structural and functional insights

Pavan V. Payghan, Indrani Bera, Dhananjay Bhattacharyya & Nanda Ghoshal [CSIR - Indian Institute of Chemical Biology]

J. Biomol. Stru. and Dyn., **34**, 1818-1837, 2016.

The γ -amino butyric acid type A receptors (GABA_A-Rs) are the key players in the mammalian brain that mediate fast inhibitory neurotransmission events. The structural integrity of these ligand-gated ion channel controls chloride ion permeability, which in turn monitors important pharmacological functions. We have employed molecular dynamics simulations accompanied by other biophysical methods to shed light on sequential and unaddressed questions like How GABA_A-R structure facilitates the entry of GABA molecules at its two orthosteric binding sites?

Ligand Docking (Cont'd)

Structure-Based Design of 3-(4-Aryl-1H-1,2,3-triazol-1-yl)-Biphenyl Derivatives as P2Y₁₄ Receptor Antagonists

Anna Junker, Ramachandran Balasubramanian, Antonella Ciancetta, Elisa Uliassi, Evgeny Kiselev, Chiara Martiriggiano, Kevin Trujillo, Giorgi Mtchedlidze, Leah Birdwell, Kyle A. Brown, T. Kendall Harden, and Kenneth A. Jacobson [National Institutes of Health, Bethesda]

Jou. Med. Chem., **59**, 6149–6168, 2016.

UDP and UDP-glucose activate the P2Y₁₄ receptor (P2Y₁₄R) to modulate processes related to inflammation, diabetes, and asthma. A computational pipeline suggested alternatives to naphthalene of a previously reported P2Y₁₄R antagonist (**3**, PPTN) using docking and molecular dynamics simulations on a hP2Y₁₄R homology model based on P2Y₁₂R structures. By reevaluating the binding of **3** to P2Y₁₄R computationally, two alternatives, i.e., alkynyl and triazolyl derivatives, were identified.

Controlling the Dissociation of Ligands from the Adenosine A_{2A} Receptor through Modulation of Salt Bridge Strength

Elena Segala, Dong Guo, Robert K. Y. Cheng, Andrea Bortolato, Francesca Deflorian, Andrew S. Doré, James C. Errey, Laura H. Heitman, Adriaan P. IJzerman, Fiona H. Marshall, and Robert M. Cooke [Heptares Therapeutics Ltd]

Jou. Med. Chem., **59**, 6470–6479, 2016.

The association and dissociation kinetics of ligands binding to proteins vary considerably, but the mechanisms behind this variability are poorly understood, limiting their utilization for drug discovery. This is particularly so for G protein-coupled receptors (GPCRs) where high resolution structural information is only beginning to emerge. Engineering the human A_{2A} adenosine receptor has allowed structures to be solved in complex with the reference compound ZM241385 and four related ligands at high resolution.

Application of Shape Similarity in Pose Selection and Virtual Screening in CSARdock2014 Exercise

Ashutosh Kumar and Kam Y. J. Zhang [RIKEN, 1-7-22 Suehiro, Tsurumi]

J.Chem. Infor. and Mod., **56**, 965–973, 2016.

To evaluate the applicability of shape similarity in docking-based pose selection and virtual screening, we participated in the CSARdock2014 benchmark exercise for identifying the correct docking pose of inhibitors targeting factor XA, spleen tyrosine kinase, and tRNA methyltransferase. This exercise provides a valuable opportunity for researchers to test their docking programs, methods, and protocols in a blind testing environment. In the CSARdock2014 benchmark exercise, we have implemented an approach that uses ligand 3D shape similarity to facilitate docking-based pose selection and virtual screening.

Evaluation of GalaxyDock Based on the Community Structure–Activity Resource 2013 and 2014 Benchmark Studies

Woong-Hee Shin, Gyu Rie Lee, and Chaok Seok [Seoul National University]

J.Chem. Infor. and Mod., **56**, 988–995, 2016.

We analyze the results of the GalaxyDock protein–ligand docking program in the two recent experiments of Community Structure–Activity Resource (CSAR), CSAR 2013 and 2014. GalaxyDock performs global optimization of a modified AutoDock3 energy function by employing the conformational space annealing method. The energy function of GalaxyDock is quite sensitive to atomic clashes. Such energy functions can be effective for sampling physically correct conformations but may not be effective for scoring when conformations are not fully optimized.

Ligand Docking (Cont'd)

Blind Pose Prediction, Scoring, and Affinity Ranking of the CSAR 2014 Dataset

Virginie Y. Martiny, François Martz, Edithe Selwa, and Bogdan I. Iorga [Institut de Chimie des Substances Naturelles]

J.Chem. Infor. and Mod., **56**, 996–1003, 2016.

The 2014 CSAR Benchmark Exercise was focused on three protein targets: coagulation factor Xa, spleen tyrosine kinase, and bacterial tRNA methyltransferase. Our protocol involved a preliminary analysis of the structural information available in the Protein Data Bank for the protein targets, which allowed the identification of the most appropriate docking software and scoring functions to be used for the rescoring of several docking conformations datasets, as well as for pose prediction and affinity ranking.

Iterative Knowledge-Based Scoring Functions Derived from Rigid and Flexible Decoy Structures: Evaluation with the 2013 and 2014 CSAR Benchmarks

Chengfei Yan, Sam Z. Grinter, Benjamin Ryan Merideth, Zhiwei Ma, and Xiaoqin Zou [Dalton Cardiovascular Research Center]

J.Chem. Infor. and Mod., **56**, 1013–1021, 2016.

In this study, we developed two iterative knowledge-based scoring functions, ITScore_pdbbind(rigid) and ITScore_pdbbind(flex), using rigid decoy structures and flexible decoy structures, respectively, that were generated from the protein–ligand complexes in the refined set of PDBbind 2012. These two scoring functions were evaluated using the 2013 and 2014 CSAR benchmarks. The results were compared with the results of two other scoring functions, the Vina scoring function and ITScore, the scoring function that we previously developed from rigid decoy structures for a smaller set of protein–ligand complexes.

CSAR Benchmark Exercise 2013: Evaluation of Results from a Combined Computational Protein Design, Docking, and Scoring/Ranking Challenge

Richard D. Smith, Kelly L. Damm-Ganamet, James B. Dunbar Jr., Aqeel Ahmed, Krishnapriya Chinnaswamy, James E. Delproposto, Ginger M. Kubish, Christine E. Tinberg, Sagar D. Khare, Jiayi Dou, Lindsey Doyle, Jeanne A. Stuckey, David Baker, and Heather A. Carlson [University of Michigan]

J.Chem. Infor. and Mod., **56**, 1022–1031, 2016.

Community Structure–Activity Resource (CSAR) conducted a benchmark exercise to evaluate the current computational methods for protein design, ligand docking, and scoring/ranking. The exercise consisted of three phases. The first phase required the participants to identify and rank order which designed sequences were able to bind the small molecule digoxigenin. The second phase challenged the community to select a near-native pose of digoxigenin from a set of decoy poses for two of the designed proteins.

Docking and Scoring with Target-Specific Pose Classifier Succeeds in Native-Like Pose Identification But Not Binding Affinity Prediction in the CSAR 2014 Benchmark Exercise

Regina Politi, Marino Convertino, Konstantin Popov, Nikolay V. Dokholyan, and Alexander Tropsha [University of North Carolina at Chapel Hill]

J.Chem. Infor. and Mod., **56**, 1032–1041, 2016.

The CSAR 2014 exercise provided an important benchmark for testing current approaches for pose identification and ligand ranking using three X-ray characterized proteins: Factor Xa (FXa), Spleen Tyrosine Kinase (SYK), and tRNA Methyltransferase (TRMD). In Phase 1 of the exercise, we employed Glide and MedusaDock docking software, both individually and in combination, with the special target-specific pose classifier trained to discriminate native-like from decoy poses. All approaches succeeded in the accurate detection of native and native-like poses.

Ligand Docking (Cont'd)

A pose prediction approach based on ligand 3D shape similarity

Ashutosh Kumar, Kam Y. J. Zhang [Center for Life Science Technologies, RIKEN]

J.Comp.Aided. Mol.des. **30**, 457-469, 2016.

Molecular docking predicts the best pose of a ligand in the target protein binding site by sampling and scoring numerous conformations and orientations of the ligand. Failures in pose prediction are often due to either insufficient sampling or scoring function errors. To improve the accuracy of pose prediction by tackling the sampling problem, we have developed a method of pose prediction using shape similarity.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 68, July, 2016.

- 1-13 **Thermo-mechanical properties of boron nitride nanoribbons: A molecular dynamics simulation study**, Sayyed Jalil Mahdizadeh, Elaheh K. Goharshadi [Ferdowsi University of Mashhad], Golnoosh Akhlagi

Thermo-mechanical properties of boron nitride nanoribbons (BNNRs) were computed using molecular dynamics simulation with optimized Tersoff empirical potential. Thermal conductivity (TC) and heat transport properties of BNNRs were calculated as functions of both temperature and nanoribbon's length.

- 14-22 **A theoretical study on the characteristics of the intermolecular interactions in the active site of human androsterone sulphotransferase: DFT calculations of NQR and NMR parameters and QTAIM analysis**, Elahe K. Astani, Emran Heshmati, Chun-Jung Chen, Nasser L. Hadipour [Tarbiat Modares University]

See Applications / Enzyme Catalysis.

- 23-28 **Efficacy of bi-component cocrystals and simple binary eutectics screening using heat of mixing estimated under super cooled conditions**, Piotr Cysewski [Nicolaus Copernicus University in Toruń]

The values of excess heat characterizing sets of 493 simple binary eutectic mixtures and 965 cocrystals were estimated under super cooled liquid condition. The application of a confusion matrix as a predictive analytical tool was applied for distinguishing between the two subsets.

- 29-38 **QM/MM investigation of the reaction rates of substrates of 2,3-dimethylmalate lyase: A catabolic protein isolated from *Aspergillus niger***, Warot Chotpatiwetchkul, Nathjanan Jongkon, Supa Hannongbua, M. Paul Gleeson [Kasetsart University]

See Methodology / QM and QM/MM.

- 39-47 **In silico designing of hyper-glycosylated analogs for the human coagulation factor IX**, Fahimeh Ghasemi, Alireza Zomorodipour, Ali Asghar Karkhane, M.Reza Khorramizadeh [Tehran University of Medical Sciences]

See Methodology / Molecular Dynamics.

- 48-56 **Prediction of three-dimensional structures and structural flexibilities of wild-type and mutant cytochrome P450 1A2 using molecular dynamics simulations**, Yurie Watanabe, Shuichi Fukuyoshi, Masahiro Hiratsuka, Noriyuki Yamaotsu, Shuichi Hirono, Ohgi Takahashi, Akifumi Oda [Kanazawa University]

See Applications / Protein Confirmation Analysis.

- 57-67 **Binding mechanism of CDK5 with roscovitine derivatives based on molecular dynamics simulations and MM/PBSA methods**, Keke Dong, Xuan Wang, Xueyu Yang, Xiaolei Zhu [Nanjing Tech University]

See Applications / Ligand Binding.

- 68-77 **High performance computing for three-dimensional agent-based molecular models**, G. Pérez-Rodríguez, M. Pérez-Pérez, F. Fdez-Riverola, A. Lourenço [Campus Universitario As Lagoas s/n]

Agent-based simulations are increasingly popular in exploring and understanding cellular systems, but the natural complexity of these systems and the desire to grasp different modelling levels demand cost-effective simulation strategies and tools. In this context, the present paper introduces novel sequential and distributed approaches for the three-dimensional agent-based simulation of individual molecules in cellular events.

- 78-86 **Molecular dynamics at the receptor level of immunodominant myelin oligodendrocyte glycoprotein 35–55 epitope implicated in multiple sclerosis**, Mary Patricia Yannakakis, Haralambos Tzoupis, Elena Michailidou, Efthimia Mantzourani, Carmen Simal, Theodore Tselios [University of Patras]

See Applications / Medicinal Chemistry and Drug Design.

- 87-94 **Theoretical and experimental investigation on the capture of H₂S in a series of ionic liquids**, Xinming Zhou, Bobo Cao, Shuangyue Liu, Xuejun Sun, Xiao Zhu, Hui Fu [China University of Petroleum]

H₂S absorptions in ionic liquids (ILs), including tetramethyl guanidinelactate (TMGL), 4-bis(2-hydroxypropyl)-1,1,3,3-tetramethyl guanidinium tetrafluoroborate ([TMGHPO₂][BF₄]) and 1-butyl-3-methylimidazolium cation ([BMIM]⁺) with the anions chloride ([Cl][−]), tetrafluoroborate ([BF₄][−]), hexafluorophosphate ([PF₆][−]), triflate ([TfO][−]), bis-(trifluoromethyl) sulfonylimide ([Tf₂N][−]), were studied in experiment and computational methods.

- 95-105 **Tuning the push–pull configuration for efficient second-order nonlinear optical properties in some chalcone derivatives**, Shabbir Muhammad [King Khalid University], Abdullah G. Al-Sehemi, Ahmad Irfan, Aijaz R. Chaudhry

Using the density functional theory methods, we effectively tune the second-order nonlinear optical (NLO) properties in some chalcone derivatives. Various unique push–pull configurations are used to efficiently enhance the intramolecular charge transfer process over the designed derivatives, which result in significantly larger amplitudes of the first hyperpolarizability as compared to their parent molecule.

- 106-113 **Centrosymmetric resonance-assisted intermolecular hydrogen bonding chains in the enol form of β-diketone: Crystal structure and theoretical study**, Eduardo F. Franca, Silvana Guillard, Drielly A. Paixão, Róbson R. Teixeira [Universidade Federal de Viçosa], Wagner L. Pereira, Javier A. Ellena

Isobenzofuran-1(3H)-ones (phtalides) are heterocycles that present a benzene ring fused to a γ-lactone functionality. This structural motif is found in several natural and synthetic compounds that present relevant biological activities. In the present investigation, the 3-(2-hydroxy-4,4-dimethyl-6-oxocyclohexen-1-yl)isobenzofuran-1(3H)-one was characterized by single-crystal X-ray analysis.

- 114-127 **Simulation of coupled folding and binding of an intrinsically disordered protein in explicit solvent with metadynamics**, Mengzhi Han, Ji Xu, Ying Ren [Chinese Academy of Sciences, Jinghai Li]

See Applications / Protein Folding.

- 128-139 **Identification of phenoxyacetamide derivatives as novel DOT1L inhibitors via docking screening and molecular dynamics simulation**, Minghao Luo, Hui Wang, Yi Zou, Shengping Zhang, Jianhu Xiao, Guangde Jiang, Yihua Zhang, Yisheng Lai [Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases]

See Applications / Medicinal Chemistry and Drug Design.

- 140-146 **Grand Canonical Monte Carlo coupled multiscale simulation for electrochemical and solvent parameters of silver halide systems in water**, V. Sudha, S. Harinipriya [SRM Research Institute], M.V. Sangaranarayanan

Grand Canonical Monte Carlo methods in conjunction with continuum Multiscale simulation to estimate the hydration energies and surface potentials of silver halides as demonstrated elsewhere is employed by incorporating random distribution of molecules, nearest neighbor distances and hydration numbers.

- 147-157 **Explaining the autoinhibition of the SMYD enzyme family: A theoretical study**, Nizar A. Al-Shar'i, Soraya M. Alnabulsi [Jordan University of Science and Technology]

See Applications / Enzyme Catalysis.

- 158-175 **Vibrational analysis and formation mechanism of typical deep eutectic solvents: An experimental and theoretical study**, Siwen Zhu, Hongping Li, Wenshuai Zhu, Wei Jiang, Chao Wang, Peiwen Wu, Qi Zhang, Huaming Li [Jiangsu University]

Deep eutectic solvents (DESs), as ionic liquid analogues for green solvents, have gained increasing attentions in chemistry. In this work, three typical kinds of DESs (ChCl/Gly, ChCl/AcOH and ChCl/Urea) were successfully synthesized and characterized by Fourier transform infrared spectroscopy (FTIR) and Raman.

- 176-183 **Perspectives for the structure-based design of acetylcholinesterase reactivators**, Rodrigo Ochoa, Carlos A. Rodriguez, Andres F. Zuluaga [Universidad de Antioquia]

See Applications / Enzyme Catalysis.

- 184-196 **New insights into the stereochemical requirements of the bradykinin B1 receptor antagonists binding**, Cecylia S. Lupala, Patricia Gomez-Gutierrez, Juan J. Perez [Universitat Politecnica de Catalunya]

See Applications / Homology Modeling.

- 197-205 **Overcoming the minimum image constraint using the closest point search**, David M. Rogers [University of South Florida]

Finding the set of nearest images of a point in a simulation cell with periodic (torus) boundary conditions is of central importance for molecular dynamics algorithms. To compute all pairwise distances closer than a given cutoff in linear time requires region-based neighbor-listing algorithms.

- 206-215 **Modeling the protonation states of β -secretase binding pocket by molecular dynamics simulations and docking studies**, Dima A. Sabbah, Haizhen A. Zhong [The University of Nebraska at Omaha]

See Applications / Enzyme Catalysis.

- 216-223 **Peptides design based on transmembrane Escherichia coli's OmpA protein through molecular dynamics simulations in water-dodecane interfaces**, Sonia M. Aguilera-Segura, Vanessa Núñez Vélez, Luke Achenie, Oscar Álvarez Solano, Rodrigo Torres, Andrés Fernando González Barrios [Universidad de los Andes]

See Applications / Surfaces, Catalysts and Material subjects.

- 224-235 **Toluene promotes lid 2 interfacial activation of cold active solvent tolerant lipase from Pseudomonas fluorescens strain AMS8**, Norhayati Yaacob, Mohd Shukuri Mohamad Ali [Universiti Putra Malaysia], Abu Bakar Salleh, Raja Noor Zaliha Raja Abdul Rahman, Adam Thean Chor Leow

The utilization of cold active lipases in organic solvents proves an excellent approach for chiral synthesis and modification of fats and oil due to the inherent flexibility of lipases under low water conditions. In order to verify whether this lipase can function as a valuable synthetic catalyst, the mechanism concerning activation of the lid and interacting solvent residues in the presence of organic solvent must be well understood. A new alkaline cold-adapted lipase, AMS8, from *Pseudomonas fluorescens* was studied for its structural adaptation and flexibility prior to its exposure to non-polar, polar aprotic and protic solvents.

- 236-251 **Multi-scale molecular dynamics study of cholera pentamer binding to a GM1-phospholipid membrane**, Akshay Sridhar, Amit Kumar, Ashok Kumar Dasmahapatra [Indian Institute of Technology Guwahati]

See Applications / Membrane Proteins.

Journal of Computational Chemistry, 37 (21), August, 2016.

- 1953–1961 **Segmentation and additive approach: A reliable technique to study noncovalent interactions of large molecules at the surface of single-wall carbon nanotubes**, Ana M. Torres, Steve Scheiner, Ajit K. Roy, Andrés M. Garay-Tapia, John Bustamante and Tapas Kar [Utah State University, Logan]

See Applications / Carbon Nanotubes.

- 1962–1972 **Assessment of semiempirical enthalpy of formation in solution as an effective energy function to discriminate native-like structures in protein decoy sets**, Gabriel Aires Urquiza-Carvalho, Wallace Duarte Fragoso and Gerd Bruno Rocha [Universidade Federal Da Paraíba]

In this work, we tested the PM6, PM6-DH+, PM6-D3, and PM7 enthalpies of formation in aqueous solution as scoring functions across 33 decoy sets to discriminate native structures or good models in a decoy set.

- 1973–1982 **Cluster analysis of molecular simulation trajectories for systems where both conformation and orientation of the sampled states are important**, Tigran M. Abramyan, James A. Snyder, Aby A. Thyparambil, Steven J. Stuart and Robert A. Latour [Clemson University]

Clustering methods have been widely used to group together similar conformational states from molecular simulations of biomolecules in solution. This study presents cluster analysis methods that are specifically designed for systems where both molecular orientation and conformation are important, and the methods are demonstrated using test cases of adsorbed proteins for validation.

1983–1992 **Three pillars for achieving quantum mechanical molecular dynamics simulations of huge systems: Divide-and-conquer, density-functional tight-binding, and massively parallel computation**, Hiroaki Nishizawa, Yoshifumi Nishimura, Masato Kobayashi, Stephan Irle and Hiromi Nakai [Waseda University]

See Methodology / QM and QM/MM.

1993–2005 **Topological analysis of the electron delocalization range**, Benjamin G. Janesko [Texas Christian University]

The electron delocalization range function $EDR(\vec{r}; d)$ (Janesko et al., J. Chem. Phys. 2014, 141, 144104) quantifies the extent to which an electron at point $\vec{r}$ in a calculated wavefunction delocalizes over distance d . This work shows how topological analysis distills chemically useful information out of the EDR. Local maxima (attractors) in the EDR occur in regions such as atomic cores, covalent bonds, and lone pairs where the wavefunction is dominated by a single orbital lobe.

2006–2016 **A critical assessment of hidden markov model sub-optimal sampling strategies applied to the generation of peptide 3D models**, A. Lamiabie, P. Thevenet and P. Tufféry [Université Paris Diderot]

See Applications / Protein Conformational Analysis.

2017–2028 **On the use of mass scaling for stable and efficient simulated tempering with molecular dynamics**, Tetsuro Nagai [Ritsumeikan University], George A. Pantelopulos, Takuya Takahashi and John E. Straub

Simulated tempering (ST) is a generalized-ensemble algorithm that employs trajectories exploring a range of temperatures to effectively sample rugged energy landscapes. A mass-scaling ST (MSST) method is presented in which the particle mass is scaled in proportion to the temperature.

Journal of Computational Chemistry, 37 (22), August, 2016.

2045–2051 **Novel enhanced applications of QSPR models: Temperature dependence of aqueous solubility**, Kyrylo Klimenko, Victor Kuz'min, Liudmila Ognichenko, Leonid Gorb, Manoj Shukla, Natalia Vinas, Edward Perkins, Pavel Polishchuk, Anatoly Artemenko and Jerzy Leszczynski [Jackson State University]

A model developed to predict aqueous solubility at different temperatures has been proposed based on quantitative structure–property relationships (QSPR) methodology.

2052–2059 **Efficient determination of accurate atomic polarizabilities for polarizeable embedding calculations**, Heiner Schröder and Tobias Schwabe [University of Hamburg]

We evaluate embedding potentials, obtained via various methods, used for polarizable embedding computations of excitation energies of para-nitroaniline in water and organic solvents as well as of the green fluorescent protein.

- 2060–2066 **A polarizable, charge transfer model of water using the drude oscillator**, Steven W. Rick [University of New Orleans]

The transfer of small amounts of charge between neighboring particles can be a significant part of interactions among particles. A model is developed for treating charge transfer (CT) combined with the Drude model for polarizability to create an efficient model for liquid water which includes both CT and polarizability.

- 2067–2080 **Torque and atomic forces for Cartesian tensor atomic multipoles with an application to crystal unit cell optimization**, Dennis M. Elking [Openeye Scientific Software]

New equations for torque and atomic force are derived for use in flexible molecule force fields with atomic multipoles. The expressions are based on Cartesian tensors with arbitrary multipole rank.

- 2081–2090 **Accurate Kohn–Sham ionization potentials from scaled-opposite-spin second-order optimized effective potential methods**, Szymon Śmiga, Fabio Della Sala, Adam Buksztel, Ireneusz Grabowski and Eduardo Fabiano [Euromediterranean Center for Nanomaterial Modelling and Technology (ECMT), Lecce]

One important property of Kohn–Sham (KS) density functional theory is the exact equality of the energy of the highest occupied KS orbital (HOMO) with the negative ionization potential of the system. In this article, we investigate the performance, in this context, of some advanced OEP methods, with special emphasis on the recently proposed scaled-opposite-spin OEP functional.

Journal of Computational Chemistry, 37 (23), September, 2016.

- 2125–2132 **Dipole and quadrupole polarizabilities of the water molecule as a function of geometry**, Oleksandr Loboda [Université de Lorraine], Francesca Ingrosso, Manuel F. Ruiz-López, Heribert Reis and Claude Millot

Dipolar, dipole–quadrupole and quadrupole–quadrupole static polarizabilities of the water molecule have been determined by ab initio calculations at coupled cluster level of theory with single, double and perturbative triple excitations CCSD(T) with an aug-cc-pVTZ basis set using a finite field and field-gradient method.

- 2133–2139 **Source function and plane waves: Toward complete bader analysis**, Christian Tantardini [Novosibirsk State University], Davide Ceresoli and Enrico Benassi

The source function (SF) is a topological descriptor that was introduced and developed by C. Gatti and R.W. Bader in 1998. The SF describes the contribution of each atom to the total electron density at a given point. This study broadens the accessibility of the SF, offering its calculation from electron densities generated by plane wave (PW) methods.

- 2140–2145 **Inverse Ubbelohde effect in the short hydrogen bond of photosystem II: Relation between H/D isotope effect and symmetry in potential energy profile**, Yusuke Kanematsu, Masanori Tachikawa and Yu Takano [Hiroshima City University]

See Methodology / QM and QM/MM.

- 2146–2156 **Charge carrier mobilities in organic semiconductor crystals based on the spectral overlap**, Vera Stehr, Reinhold F. Fink, Carsten Deibel and Bernd Engels [Universität Würzburg]

The prediction of substance-related charge-transport properties is important for the tailoring of new materials for organic devices, such as organic solar cells. Assuming a hopping process, the Marcus theory is frequently used to model charge transport. Here another approach, which is already widely used for exciton transport, is adapted to charge transport.

2157–2162 **The application of cholesky decomposition in valence bond calculation**, Xiping Gong, Zhenhua Chen and Wei Wu [Xiamen University]

The Cholesky decomposition (CD) technique, used to approximate the two-electron repulsion integrals (ERIs), is applied to the valence bond self-consistent field (VBSCF) method. Test calculations on ethylene, $C_{2n}H_{2n+2}$, and $C_{2n}H_{4n-2}$ molecules ($n = 1-7$) show that the performance of the VBSCF method is much improved using the CD technique, and thus, the integral transformation from basis functions to VB orbitals is no longer the bottleneck in VBSCF calculations.

Journal of Computational Chemistry, 37 (24), September, 2016.

2171–2180 **Efficient implementation of constant pH molecular dynamics on modern graphics processors**, Evan J. Arthur and Charles L. Brooks III [University of Michigan, Ann Arbor]

See Applications / Protein Dynamics.

2181–2192 **Optical response of the Cu_2S_2 diamond core in $Cu_2II(NGuaS)_2Cl_2$** , Matthias Witte, Benjamin Grimm-Lebsanft, Arne Goos, Stephan Binder, Michael Rübhausen, Martin Bernard, Adam Neuba, Serge Gorelsky, Uwe Gerstmann, Gerald Henkel, Wolf Gero Schmidt and Sonja Herres-Pawlis [RWTH Aachen University]

Density functional theory (DFT) and time-dependent DFT calculations are presented for the dicopper thiolate complex $Cu_2(NGuaS)_2Cl_2$ [$NGuaS=2-(1,1,3,3\text{-tetramethylguanidino})$ benzenethiolate] with a special focus on the bonding mechanism of the $Cu_2S_2Cl_2$ core and the spectroscopic response.

2193–2201 **Performance of heterogeneous computing with graphics processing unit and many integrated core for hartree potential calculations on a numerical grid**, Sunghwan Choi, Oh-Kyoung Kwon, Jaewook Kim and Woo Youn Kim [Department of Chemistry, KAIST]

We investigated the performance of heterogeneous computing with graphics processing units (GPUs) and many integrated core (MIC) with 20 CPU cores ($20 \times CPU$). As a practical example toward large scale electronic structure calculations using grid-based methods, we evaluated the Hartree potentials of silver nanoparticles with various sizes (3.1, 3.7, 4.9, 6.1, and 6.9 nm) via a direct integral method supported by the sinc basis set.

2202–2211 **Structure, stability, and nature of bonding in carbon monoxide bound EX_3^+ complexes ($E = \text{group 14 element}$; $X = H, F, Cl, Br, I$)**, Manas Ghara, Sudip Pan, Anand Kumar, Gabriel Merino [Indian Institute of Technology, Kharagpur] and Pratim K. Chattaraj

A density functional theory study is performed to predict the structures and stability of carbon monoxide (CO) bound EX_3^+ ($E = C, Si, Ge, Sn, Pb$; $X = H, F, Cl, Br, I$) complexes. The possibility of bonding through both C- and O-sides of CO is considered.

- 2212–2219 **Theoretical study on photooxidation mechanism of ruthenium complex $[\text{Ru(II)}-(\text{bpy})_2(\text{TMBiimH}_2)]^{2+}$ with molecular oxygen**, Li-Hong Liu, Dan Wu, Shu-Hua Xia and Ganglong Cui [Beijing Normal University, Beijing]

Photoinduced reactions of ruthenium complexes with molecular oxygen have attracted a lot of experimental attention; however, the reaction mechanism remains elusive. In this work, we have used the density functional theory method to scrutinize the visible-light induced photooxidation mechanism of the ruthenium complex $[\text{Ru(II)}-(\text{bpy})_2(\text{TMBiimH}_2)]^{2+}$ (bpy: 2, 2-bipyridine and TMBiimH₂: 4, 5, 4, 5-tetramethyl-2, 2-biimidazole) initiated by the attack of molecular oxygen. The present computational results not only explain very well recent experiments, also provide.

- 2220–2227 **Thermodynamic compatibility of actives encapsulated into PEG-PLA nanoparticles: In Silico predictions and experimental verification**, Andreas Erlebach, Timm Ott, Christoph Otzen, Stephanie Schubert, Justyna Czaplewska, Ulrich S. Schubert and Marek Sierka [Friedrich Schiller University Jena]

See Applications / Protein Dynamics.

- 2228–2241 **Design of [2]rotaxane through image threshold segmentation of electrostatic potential image**, Pingying Liu, Qiufeng Chen and Jing Ma [Nanjing University, Nanjing]

An electrostatic potential (ESP)-based image segmentation method has been used to estimate the ability of proton donation and acceptance involved in ring-rod recognition. The relative binding strength of [2]rotaxane has also been further estimated from the difference of the characteristic image-segmentation derived ESP between proton donor and proton acceptor.

Journal of Molecular Modeling, 22 (8), August, 2016.

- 172 **Sodium-ion electrolytes based on ionic liquids: a role of cation-anion hydrogen bonding**, Vitaly V. Chaban [Federal University of São Paulo], Nadezhda A. Andreeva

Recent success of the sodium-ion batteries fosters an academic interest for their investigation. Room-temperature ionic liquids (RTILs) constitute universal solvents providing non-volatility and non-flammability to electrolytes. In the present work, we consider four families of RTILs as prospective solvents for NaBF₄ and NaNO₃ with an inorganic salt concentration of 25 and 50 mol%.

- 173 **Efficient modulation of optical and electrical properties of X-shaped thermally activated delayed fluorescence emitters by substitution**, Jianzhong Fan, Xin Wang, Lili Lin, Chuankui Wang [Shandong Normal University]

A series of X-shaped thermally activated delayed fluorescence (TADF) emitters are systematically studied by first-principles calculations. Effects of the cyano group adding to the acceptor unit and the hydroxyl group adding to the donor part on the optical and electrical properties are analyzed.

- 174 **The inner-induced effects of YCN in C₇₆ on the structures and nonlinear optical properties**, Feng-Wei Gao, Hong-Liang Xu, Zhong-Min Su [Northeast Normal University]

Very recently, an unprecedented novel monometallic cluster of fullerenes entrapping a yttrium cyanide (YCN) cluster inside a popular C₈₂ cage YCN@Cs(6)-C₈₂ was synthesized and characterized. Inspired by this investigation, four non-IPR YCN@C₁(17459)-C₇₆, YCN@C_{2v}(19138)-C₇₆, YCN@C₂(17646)-C₇₆, and

YCN@C₁(17894)-C₇₆ (1, 2, 3, and 4) containing a pair of adjacent pentagons are designed to explore the encapsulated molecular effect on their interaction energies and nonlinear optical properties.

- 175 **Van der Waals molecular interactions in the organic functionalization of graphane, silicane, and germanane with alkene and alkyne molecules: a DFT-D2 study**, Pamela Rubio-Pereda [Centro de Investigación Científica y de Educación Superior de Ensenada 3918], Noboru Takeuchi

Density functional theory with the addition of a semi-empirical dispersion potential was applied to the conventional Kohn–Sham energy to study the adsorption of alkene and alkyne molecules on hydrogen-terminated two-dimensional group IV systems (graphane, silicane, and germanane) by means of a radical-initiated reaction.

- 176 **Investigating the substrate binding mechanism of sulfotransferase 2A1 based on substrate tunnel analysis: a molecular dynamics simulation study**, Li Zhao, Pupu Zhang, Shiyang Long, Linlin Wang, Hanyong Jin, Weiwei Han, Pu Tian [Jilin University]

See Applications / Enzyme Catalysis.

- 177 **Examination of the quality of various force fields and solvation models for the equilibrium simulations of GA88 and GB88**, Juan Zeng [Peking University Shenzhen Graduate School], Yongxiu Li, John Z.H. Zhang, Ye Mei

See Methodology / Potentials and Parameters.

- 178 **Pharmacophore development and screening for discovery of potential inhibitors of ADAMTS-4 for osteoarthritis therapy**, Priyanka Verma, Krishna Dalal, Madhu Chopra [Dr. B. R. Ambedkar Center for Biomedical Research]

See Applications / Medicinal Chemistry and Drug Design.

- 179 **Influence of the chelator structures on the stability of Re and Tc tricarbonyl complexes with iminodiacetic acid tridentate ligands: a computational study**, Daniel Hernández-Valdés, Zalua Rodríguez-Riera, Alicia Díaz-García, Eric Benoist, Ulises Jáuregui-Haza [Instituto Superior de Tecnología y Ciencias Aplicadas]

See Methodology / QM and QM/MM.

- 180 **Homology modeling, substrate docking, and molecular simulation studies of mycobacteriophage Che12 lysin A**, Shainaba A Saadhali, Sameer Hassan, Luke Elizabeth Hanna, Uma Devi Ranganathan, Vanaja Kumar [National Institute for Research in Tuberculosis]

See Applications / Medicinal Chemistry and Drug Design.

- 181 **The role of OH...O and CH...O hydrogen bonds and H...H interactions in ethanol/methanol–water heterohexamers**, Sol M. Mejía [Pontificia Universidad Javeriana], Juan F. Espinal, Matthew J. L. Mills, Fanor Mondragón

Bioethanol is one of the world's most extensively produced biofuels. However, it is difficult to purify due to the formation of the ethanol–water azeotrope. Knowledge of the azeotrope structure at the molecular level can help to improve existing purification methods. In order to achieve a better understanding of this azeotrope structure, the characterization of (ethanol)₅–water heterohexamers was carried out by analyzing the results of electronic structure calculations performed at the B3LYP/6-31+G(d) level.

- 182 **The charge mobilities in fused ring Oligothiophenes and their derivatives: influence of molecular structures,** Yajuan Liu, Xiaoyan Liu, Jindou Huang, Jianyong Liu, Shijie Xie, Yujun Zheng [Shandong University]

Fused ring oligothiophenes and their derivatives, as active organic semiconductors, are widely used in electronic devices. The influence of molecular conjunction length on reorganization energy, electronic coupling and charge mobility of two fused ring oligothiophenes are investigated theoretically.

- 183 **Structural determination of complex natural products by quantum mechanical calculations of ¹³C NMR chemical shifts: development of a parameterized protocol for terpenes,** Ana Carolina Ferreira de Albuquerque, Daniel Joras Ribeiro, Mauro Barbosa de Amorim [Universidade Federal do Rio de Janeiro]

Nuclear magnetic resonance (NMR) spectroscopy is one of the most important tools for determining the structures of organic molecules. In this work, we present the development of a protocol for ¹³C chemical shift calculations of terpenes, a class of natural products that are widely distributed among plant species and are very important due to their biological and pharmacological activities.

- 184 **Computational investigation on MB_n (M = Li-Cs, Be-Ba, Sc-La and Ti; n = 28 and 38),** Qianhui Xu, Chang Liu, Le Yang, Peng Jin, Chengchun Tang, Zhongfang Chen [University of Puerto Rico]

Differing from the weakly antiaromatic B₈₀ buckyball, the medium-sized C₁–B₂₈ and D_{2h}–B₃₈, as well as their mono- to tetra-anions, are highly aromatic, as indicated by the negative nucleus-independent chemical shifts (NICs) at their cage centers. We carried out systematic density functional theory (DFT) computations on the structures, stabilities and electronic properties of metalloborofullerenes MB_n (M = Li, Na, K, Rb, Cs, Be, Mg, Ca, Sr, Ba, Sc, Y, La and Ti; n = 28 and 38).

- 185 **A probabilistic approach for estimating water permeability in pressure-driven membranes,** Linkel K. Boateng, Ramin Madarshahian, Yeomin Yoon, Juan M. Caicedo, Joseph R. V. Flora [University of South Carolina]

A probabilistic approach is proposed to estimate water permeability in a cellulose triacetate (CTA) membrane. Water transport across the membrane is simulated in reverse osmosis mode by means of non-equilibrium molecular dynamics (MD) simulations.

- 186 **Investigating the mechanism of the selective hydrogenation reaction of cinnamaldehyde catalyzed by Pt_n clusters,** Laicai Li [Sichuan Normal University], Wei Wang, Xiaolan Wang, Lin Zhang

Cinnamaldehyde (CAL) belongs to the group of aromatic α,β -unsaturated aldehydes; the selective hydrogenation of CAL plays an important role in the fine chemical and pharmaceutical industries. Using Pt_n clusters as catalytic models, we studied the selective hydrogenation reaction mechanism for CAL catalyzed by Pt_n (n = 6, 10, 14, 18) clusters by means of B3LYP in density functional theory at the 6-31+ G(d) level (the LanL2DZ extra basis set was used for the Pt atom).

- 187 **Z-Isomers of (4 α →6'', 2 α →O→1'')-phenylflavan substituted with R'=R=OH. Conformational properties, electronic structure and aqueous solvent effects**, Erika N. Bentz, Alicia B. Pomilio, Rosana M. Lobayan [Universidad Nacional del Nordeste]

Procyanidins are highly hydroxylated polymers known as antioxidant compounds, thereby exhibiting beneficial effects. These compounds are protective agents against oxidative stress and the damage induced by free radicals in membranes and nucleic acids. This paper describes a study of the conformational space of (4 α →6'', 2 α →O→1'')-phenylflavan substituted with R'=R=OH as part of a larger study of similar structures with different substitutions.

- 188 **Effects of ligand binding on the mechanical stability of protein GB1 studied by steered molecular dynamics simulation**, Ji-Guo Su, Shu-Xin Zhao, Xiao-Feng Wang, Chun-Hua Li, Jing-Yuan Li [Chinese Academy of Science]

See Applications / Protein Dynamics.

- 189 **Effects of the adsorption of alkali metal oxides on the electronic, optical, and thermodynamic properties of the Mg₁₂O₁₂nanocage: a density functional theory study**, Asghar Mohammadi Hesari, Hamid Reza Shamlouei, [Lorestan University] Ali Raoof Toosi

The effect of alkali metal oxides M_nO (M = Li, Na, K; n = 2, 3, 4) on the geometric, electronic, and linear and nonlinear optical properties of the Mg₁₂O₁₂ nanocage was investigated by density-functional-based methods.

- 190 **Dimerization of quercetin, Diels-Alder vs. radical-coupling approach: a joint thermodynamics, kinetics, and topological study**, Isabelle Fourré, Florent Di Meo [Sorbonne Universités Sorbonne Universités], Pavlína Podloucká, Michal Otyepka, Patrick Trouillas

Quercetin is a prototypical antioxidant and prominent member of flavonoids, a large group of natural polyphenols. The oxidation of quercetin may lead to its dimerization, which is a paradigm of the more general polyphenol oligomerization. There exist two opposing mechanisms to describe the dimerization process, namely radical-coupling or Diels-Alder reactions. This work presents a comprehensive rationalization of this dimerization process, acquired from density functional theory (DFT) calculations.

- 191 **TD-DFT calculations and thermal effects on conformers of calmagite in protic solvents varying the degree of protonation**, Z. N. Cisneros-García, V. F. Marañón-Ruiz, J. G. Rodríguez-Zavala [Centro Universitario de los Lagos Universidad de Guadalajara]

The main absorption peaks were obtained for 1-(1-hydroxy-4-methyl-2-phenylazo)-2-naphthol-4-sulfonic acid. Generalized gradient approximation, hybrid, semi-empirical, and Coulomb attenuating methods were utilized to compare theoretical electronic transitions and experimental absorption spectra at different pH. In order to find the most populated conformer, thermal effects on stability calculations were investigated to obtain molar fractions of possible isomers present at room and higher temperature.

- 192 **Modulating the strength of tetrel bonding through beryllium bonding**, Mingxiu Liu, Li Yang, Qingzhong Li [Yantai University], Wenzuo Li, Jianbo Cheng, Bo Xiao, Xuefang Yu

Quantum chemical calculations were performed to investigate the stability of the ternary complexes BeH₂⋯XMH₃⋯NH₃ (X = F, Cl, and Br; M = C, Si, and Ge) and the corresponding binary complexes at the atomic level.

- 193 **Reexamination of structures, stabilities, and electronic properties of holmium-doped silicon clusters HoSi_n ($n = 12-20$)**, Liyuan Hou, Jucai Yang [Inner Mongolia University of Technology], Yuming Liu

The total energies, growth patterns, equilibrium geometries, relative stabilities, hardnesses, intramolecular charge transfer, and magnetic moments of HoSi_n ($n = 12-20$) clusters have been reexamined theoretically using two different density functional schemes in combination with relativistic small-core Stuttgart effective core potentials (ECP28MWB) for the Ho atoms.

- 194 **A relativistic DFT probe of polypyrrolic macrocyclic diuranium(III) complexes with terminal solvents and iodines**, Dong-Mei Su, Xiu-Jun Zheng, Yuan-Ru Guo, Qing-Jiang Pan [Heilongjiang University]

Relativistic density functional theory finds that two isomers of a diuranium(III) complex of a polypyrrolic macrocycle (H_4L) feature active sites on uranium moieties, allowing for their potential application in activating industrially and economically important small molecules. To address this, a series of adducts $[(\text{X})_n\text{U}_2(\text{L})]^{(2-m)+}$ ($\text{X} = \text{THF}$, I^- and HI ; $n = 1$ and 2 ; $m = 0, 1$ and 2) have been examined.

- 195 **A theoretical investigation of the interactions between hydroxyl-functionalized ionic liquid and water/methanol/dimethyl sulfoxide**, Shuang Zhao, XinZhe Tian, YunLai Ren, JianJi Wang [Henan University of Science and Technology], JunNa Liu, YunLi Ren

Density functional calculations have been used to investigate the interactions of 1-(2-hydroxyethyl)-3-methylimidazolium $[\text{C}_2\text{OHmim}]^+$ -based ionic liquids (hydroxyl ILs) with water (H_2O), methanol (CH_3OH), and dimethyl sulfoxide (DMSO).

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- 196 **Molecular cloning and in silico characterization of knottin peptide, U2-SCRTX-Lit2, from brown spider (*Loxosceles intermedia*) venom glands**, Gabriel Otto Meissner, Pedro Túlio de Resende Lara, Luis Paulo Barbour Scott, Antônio Sérgio Kimus Braz, Daniele Chaves-Moreira, Fernando Hitomi Matsubara, Eduardo Mendonça Soares, Dilza Trevisan-Silva, Luiza Helena Gremski, Silvio. Sanches Veiga, Olga Meiri Chaim [Federal University of Paraná]

See Applications / Protein Secondary Structure.

- 197 **Theoretical study of coupling p-aminothiophenol to hydroazo- and azo-adducts on Au(111)**, Xiufeng Lang [Hebei Normal University of Science and Technology], Yanhong Liang, Siyan Liu, Shanshan Zhao, Woon-Ming Lau

Aminothiophenol/Au(111) has been adopted as an exemplary model in plasmonics research, including surface-enhanced Raman spectroscopy, due to its high plasmonic-induced spectral-signal enhancement. The present work was aimed at clarifying whether aminothiophenol on Au(111) is chemically stable in the absence of any photo- and plasmonic-induced effects.

- 198 **Effect of electric charging on the velocity of water flow in CNT**, Hossein Reza Abbasi, S. M. Hossein Karimian [Amirkabir University of Technology (Tehran Polytechnic)]

See Applications / Carbon Nanotubes.

- 199 **Insight into the kinetics and thermodynamics of the hydride transfer reactions between quinones and lumiflavin: a density functional theory study**, Clorice R. Reinhardt, Tanner C. Jaglinski, Ashly M. Kastenschmidt, Eun H. Song, Adam K. Gross, Alyssa J. Krause, Jonathan M. Gollmar, Kristin J. Meise, Zachary S. Stenerson, Tyler J. Weibel, Andrew Dison, Mackenzie R. Finnegan, Daniel S. Griesi, Michael D. Heltne, Tom G. Hughes, Connor D. Hunt, Kayla A. Jansen, Adam H. Xiong, Sanchita Hati, Sudeep Bhattacharyya [University of Wisconsin-Eau Claire]

The kinetics and equilibrium of the hydride transfer reaction between lumiflavin and a number of substituted quinones was studied using density functional theory. The impact of electron withdrawing/donating substituents on the redox potentials of quinones was studied.

- 200 **Photoinduced hydrogen-bonding dynamics**, Tian-shu Chu [Qingdao University], Jinmei Xu

Hydrogen bonding dynamics has received extensive research attention in recent years due to the significant advances in femtolaser spectroscopy experiments and quantum chemistry calculations. In this article, we review the combined experimental and theoretical studies focusing on the ultrafast electronic and vibrational hydrogen bonding dynamics.

- 201 **In-silico studies on DegP protein of Plasmodium falciparum in search of anti-malarials**, Drista Sharma, Rani Soni, Sachin Patel, Deepti Joshi, Tarun Kumar Bhatt [Central University of Rajasthan]

See Applications / Medicinal Chemistry and Drug Design.

- 202 **Evolution of the hydrogen-bonding motif in the melamine–cyanuric acid co-crystal: a topological study**, Andre N. Petelski, Nelida M. Peruchena, Gladis L. Sosa [Universidad Tecnológica Nacional]

The melamine (M)/cyanuric acid (CA) supramolecular system is perhaps one of the most exploited in the field of self-assembly because of the high complementarity of the components. However, it is necessary to investigate further the factors involved in the assembly process. In this study, we analyzed a set of 13 M_n/CA_m clusters (with $n, m = 1, 2, 3$), taken from crystallographic data, to characterize the nature of the hydrogen bonds involved in the self-assembly of these components as well as to provide greater understanding of the phenomenon.

- 203 **The dopamine D₂ receptor dimer and its interaction with homobivalent antagonists: homology modeling, docking and molecular dynamics**, Agnieszka A. Kaczor [Medical University of Lublin], Manuela Jörg, Ben Capuano

See Applications / Homology Modeling.

- 204 **H₂ adsorption and dissociation on PdO(101) films supported on rutile TiO₂ (110) facet: elucidating the support effect by DFT calculations**, Xiongfei Sun, Xing Peng, Xianglan Xu, Hua Jin, Hongming Wang, Xiang Wang [Nanchang University]

To explore metal oxide–support interactions and their effect, H₂ adsorption and dissociation on PdO(101)/TiO₂(110) films with different film thicknesses, in comparison with that on pure PdO(101) surface without TiO₂(110) support, were studied by density functional theory calculation. A monolayer PdO(101) film supported on TiO₂ facet shows different properties to a pure PdO(101) surface.

- 205 **A theoretical study on monoatomic BN nanochains and nanorings**, Rouhollah Namazi Rizi [Islamic Azad University], Maziar Noei

Boron nitride (BN) nanochains were successfully synthesized recently. In this work, we investigate the electronic, energetic, and structural properties of BN nanochains and nanorings by means of density functional theory calculations. Our calculations support the experimental findings and offer additional physical insights into these new nanostructured materials.

- 206 **Fibpredictor: a computational method for rapid prediction of amyloid fibril structures**, Hamed Tabatabaei Ghomi, Elizabeth M. Topp, Markus A. Lill [Purdue University]

Amyloid fibrils are important in diseases such as Alzheimer's disease and Parkinson's disease, and are also a common instability in peptide and protein drug products. Despite their importance, experimental structures of amyloid fibrils in atomistic detail are rare. To address this limitation, we have developed a novel, rapid computational method to predict amyloid fibril structures (Fibpredictor).

- 207 **Formation of β -cyclodextrin complexes in an anhydrous environment**, Hocine Sifaoui, Ali Modarressi, Pierre Magri, Anna Stachowicz-Kuśnierz, Jacek Korchowiec [Jagiellonian University], Marek Rogalski

The formation of inclusion complexes of β -cyclodextrin was studied at the melting temperature of guest compounds by differential scanning calorimetry. The complexes of long-chain n-alkanes, polyaromatics, and organic acids were investigated by calorimetry and IR spectroscopy.

- 208 **Theoretical insight into the interaction between SnX_2 ($\text{X} = \text{H}, \text{F}, \text{Cl}, \text{Br}, \text{I}$) and benzene**, Piotr Matczak [University of Łódź]

For a series of five model complexes composed of a singlet SnX_2 molecule ($\text{X} = \text{H}, \text{F}, \text{Cl}, \text{Br}, \text{I}$) and a benzene molecule, the first-principles calculations of their energetics and the analysis of their electron density topology have been performed.

- 209 **DFT/TDDFT investigation on the chemical reactivities, aromatic properties, and UV-Vis absorption spectra of 1-butoxy-4-methoxybenzenepillar[5]arene constitutional isomers**, Jian Zhang [Shanxi Normal University], Shuqing Ren

We investigate the chemical reactivities, aromatic properties, and UV-Vis absorption spectra of four constitutional isomers of 1-butoxy-4-methoxybenzenepillar[5]arene with the DFT and TDDFT methods.

- 210 **Structure and dynamics of solvated hydrogenoxalate and oxalate anions: a theoretical study**, Ondřej Kroutil, Babak Minofar, Martin Kabeláč [University of South Bohemia]

Hydrogenoxalate (charge -1) and oxalate (charge -2) anions and their solvated forms were studied by various computational techniques. Ab initio quantum chemical calculations in gas phase, in implicit solvent and microsolvated (up to 32 water molecules) environment were performed in order to explore a potential energy surface of both anions.

- 211 **Theoretical study on the oligomerization mechanisms of bihydroxysilicone**, Xueli Cheng [Taishan University], Yanyun Zhao

Bihydroxysilicone $\text{SiO}(\text{OH})_2$ is the simplest silicone monomer and can be condensed to various silica materials with diverse properties. The oligomerization mechanisms of $\text{SiO}(\text{OH})_2$ were investigated systematically at B3LYP/6-311++G(d,p) level.

- 212 **Conformational and reactivity study of dithiophenyl-fucosyl ketals with theoretical chemical methods,**
Angel E. Bañuelos-Hernandez, Hugo A. García-Gutiérrez, Mabel Fragoso-Serrano, José Alberto Mendoza-Espinoza [Universidad Autónoma de la Ciudad de México]

Carbohydrates can be used as substrates to synthesize new complex molecules; these molecules contain several chiral centers that can be used in organic synthesis. d-Fucose diphenyl thioacetal reacts differentially with acetone, and this paper describes a study of the mechanism of this reaction using theoretical chemistry methods.

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About 125 Papers from more than 30 Journals are cited.

1 APPLICATIONS (87)

Page 2

1.1 Small Molecules (23)

General and Model Systems	Page 2	Med. Chem. And Drug	Page 4
Water and Solvation	Page 2	QSAR	Page 7
Organic Solvents	Page 3	Zeolites	Page 8

1.2 Biopolymers (64)

Bioinformatics and Cheminformatics	Page 8	Enzyme Catalysis	Page 18
Protein Side Chain Confirmation Prediction	Page 10	Protein-Protein Interactions	Page 19
Protein Conformational Analysis	Page 10	Membrane Proteins	Page 20
Protein Structure Analysis	Page 11	Protein Folding	Page 23
Protein Dynamics	Page 12	Protein-Nucleic Acids	Page 24
Free Energy Calculations	Page 13	Nucleic Acids	Page 25
Ligand Binding	Page 14		

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (27)

Page 25

QSAR	Page 25	QM & QM/MM	Page 29
Potentials and Parameters	Page 26	Comparative or Homology	Page 31
Molecular Dynamics	Page 27	Ligand Docking	Page 31
Free Energy Perturbation	Page 29		

3 JOURNAL REVIEWS (6)

Page 33

Journal of Molecular Graphics and Modeling, 69, September, 2016.
 Journal of Computational Chemistry, 37 (25), September, 2016.
 Journal of Computational Chemistry, 37 (26, 27, 28), October, 2016.
 Journal of Molecular Modeling, 22 (10), October, 2016.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 42

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Optimization of Analytical Potentials for Coarse-Grained Biopolymer Models

Paolo Mereghetti, Giuseppe Maccari, Giulia Lia Beatrice Spampinato, and Valentina Tozzini[Scuola Normale Superiore]

J. Phys. Chem. B., **120**, 8571–8579, 2016.

The increasing trend in the recent literature on coarse grained (CG) models testifies their impact in the study of complex systems. However, the CG model landscape is variegated: even considering a given resolution level, the force fields are very heterogeneous and optimized with very different parametrization procedures. Along the road for standardization of CG models for biopolymers, here we describe a strategy to aid building and optimization of statistics based analytical force fields and its implementation in the software package AsParaGS (Assisted Parameterization platform for coarse Grained modelS).

Water and Solvation

Hydration Dynamics of a Peripheral Membrane Protein

Olivier Fisette, Christopher Päslock, Ryan Barnes, J. Mario Isas, Ralf Langen, Matthias Heyden, Songi Han, and Lars V. Schäfer [Ruhr-University]

J. Am. Chem. Soc., **138**, 11526–11535, 2016.

Water dynamics in the hydration shell of the peripheral membrane protein annexin B12 were studied using MD simulations and Overhauser DNP-enhanced NMR. We show that retardation of water motions near phospholipid bilayers is extended by the presence of a membrane-bound protein, up to around 10 Å above that protein. Near the membrane surface, electrostatic interactions with the lipid head groups strongly slow down water dynamics, whereas protein-induced water retardation is weaker and dominates only at distances beyond 10 Å from the membrane surface.



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Water and Solvation (Cont'd)

Enthalpic and Entropic Contributions to Hydrophobicity

Michael Schauperl, Maren Podewitz, Birgit J. Waldner, and Klaus R. Liedl [University of Innsbruck, Innrain]

J. Chem. Theor. and Comp, **12**, 4600–4610, 2016.

Hydrophobic hydration plays a key role in a vast variety of biological processes, ranging from the formation of cells to protein folding and ligand binding. Hydrophobicity scales simplify the complex process of hydration by assigning a value describing the averaged hydrophobic character to each amino acid. Previously published scales were not able to calculate the enthalpic and entropic contributions to the hydrophobicity directly. We present a new method, based on Molecular Dynamics simulations and Grid Inhomogeneous Solvation Theory, that calculates hydrophobicity from enthalpic and entropic contributions.

Water molecules inside protein structure affect binding of monosaccharides with HIV-1 antibody 2G12

Kaori Ueno-Noto [Kitasato University, Minami-Ku] and Keiko Takano

J. Comp. Chem., **37**, 2341–2348, 2016.

Water molecules inside biomolecules constitute integral parts of their structure and participate in the functions of the proteins. Some of the X-ray crystallographic data are insufficient for analyzing a series of ligand–protein complexes in the same condition. We theoretically investigated antibody binding abilities of saccharide ligands and the effects of the inner water molecules of ligand–antibody complexes. Classical molecular dynamics and quantum chemical simulations using a model with possible water molecules inside the protein were performed with saccharide ligands and Human Immunodeficiency Virus 1 neutralizing antibody 2G12 complexes to estimate how inner water molecules of the protein affect the dynamics of the complexes as well as the ligand–antibody interaction.

Organic Solvents

Simulation of Singlet Exciton Diffusion in Bulk Organic Materials

Julian J. Kranz and Marcus Elstner [Karlsruhe Institute of Technology]

J. Chem. Theor. and Comp, **12**, 4209–4221, 2016.

We present a scheme for nonadiabatic direct dynamics simulation of Frenkel exciton diffusion in bulk molecular systems. The fluctuations of exciton couplings caused by the molecular motion can crucially influence exciton transport in such materials. This effect can be conveniently taken into account by computing the exciton couplings along molecular dynamics trajectories, as shown recently. In this work, we combine Molecular Dynamics simulations with a Frenkel Hamiltonian into a combined quantum-mechanical/molecular mechanics approach in order to allow for a simultaneous propagation of nuclear and electronic degrees of freedom using nonadiabatic dynamics propagation schemes.

Medicinal Chemistry and Drug Design

In-silico identification of inhibitors against mutated BCR-ABL protein of chronic myeloid leukemia: a virtual screening and molecular dynamics simulation study

Himansu Kumar, Utkarsh Raj, Saurabh Gupta & Pritish Kumar Varadwaj [Indian Institute of Information Technology – Allahabad]

J. Biomol. Stru. And Dyn., **34**, 2171-2183, 2016.

Aberrant and proliferative expression of the oncogene BCR-ABL in the bone marrow cells had been proven as the prime cause of chronic myeloid leukemia (CML). It has been established that tyrosine kinase domain of BCR-ABL protein is a potential therapeutic target for the treatment of CML. Imatinib is considered as a first-generation drug that can inhibit the enzymatic action by inhibiting the ATP binding with BCR-ABL protein. Later on, insensitivity of CML cells towards Imatinib has been observed may be due to mutation in tyrosine kinase domain of the ABL receptor. By taking into account of bioavailability and resistance developed, there is an utmost need to find some more inhibitors for the mutated ABL tyrosine kinase protein.

Virtual screening, docking, and dynamics of potential new inhibitors of dihydrofolate reductase from *Yersinia pestis*

Leonardo da Costa Bastos, Felipe Rodrigues de Souza, Ana Paula Guimarães, Mehdi Sirouspour, Teobaldo Ricardo Cuya Guizado, Pat Forgione, Teodorico Castro Ramalho & Tanos Celmar Costa França [Military Institute of Engineering, Rio de Janeiro]

J. Biomol. Stru. And Dyn., **34**, 2184-2198, 2016.

In the present work, we propose to design drugs that target the enzyme dihydrofolate reductase (DHFR) as a means of a novel drug therapy against plague. Potential inhibitors of DHFR from *Yersinia pestis* (YpDHFR) were selected by virtual screening and subjected to docking, molecular dynamics (MD) simulations, and Poisson–Boltzmann surface area method, in order to evaluate their interactions in the active sites of YpDHFR and human DHFR (HsDHFR).

E-pharmacophore filtering and molecular dynamics simulation studies in the discovery of potent drug-like molecules for chronic kidney disease

Selvaraman Nagamani, Karthikeyan Muthusamy [Allagappa University] & J. John Marshall

J. Biomol. Stru. And Dyn., **34**, 2233-2250, 2016.

Chronic kidney disease (CKD) is a prominent health issue reported globally. The level of the vitamin D receptor (VDR) and cytochrome P450 enzyme 24-hydroxylase (CYP24A1) are crucial in the pathogenesis of secondary hyperparathyroidism (sHPT) in CKD. An elevated expression of the CYP24A1 leads to the deficiency of vitamin D and resistance to vitamin D therapy. In this study, combined molecular docking and pharmacophore filtering were employed to identify compounds better than CTA-018. A huge set of 9127 compounds from Sweet Lead database were docked into the active site of VDR using Glide XP program.

Fragment based G-QSAR and molecular dynamics based mechanistic simulations into hydroxamic-based HDAC inhibitors against spinocerebellar ataxia

Siddharth Sinha, Chetna Tyagi, Sukriti Goyal, Salma Jamal, Pallavi Somvanshi [Jawaharlal Nehru University] & Abhinav Grover

J. Biomol. Stru. And Dyn., **34**, 2281-2295, 2016.

Expansion of polyglutamine (CAG) triplets within the coding gene ataxin 2 results in transcriptional repression, forming the molecular basis of the neurodegenerative disorder named spinocerebellar ataxia type-2 (SCA2). HDAC inhibitors (HDACi) have been elements of great interest in polyglutamine disorders such as Huntington's and Ataxia's. In this study, we have selected hydroxamic acid derivatives as HDACi and performed fragment-based G-QSAR, molecular docking studies and molecular dynamics simulations for elucidating the dynamic mode of action of HDACi with His-Asp catalytic dyad of HDAC4. The model was statistically validated to establish its predictive robustness.

Medicinal Chemistry and Drug Design (Cont'd)

Development and targeting of transcriptional regulatory network controlling FLU1 activation in *Candida albicans* for novel antifungals

AnubhutiJha, Awanish Kumar [National Institute of Technology Raipur]

J. Mol.Graph. and Mod., **69**,1-7, 2016.

Candidiasis caused by primarily *Candida albicans* poses serious threat due to dry pipeline and ineffective antifungal strategy against resistance. In this study we propose to target genes involved in efflux mediated Multi drug resistance. The main objective of this study was to understand the regulatory interactions responsible for activating a major MFS transporter gene of *Candida albicans*. Another aim was to identify the docking effect of certain antifungal compounds upon the transcription factor effectively controlling *FLU1*.

Theoretical study on the metabolic mechanisms of levomepromazine by cytochrome P450

Yongting Wang, Qiu Chen, ZhiyuXue, Yan Zhang, Zeqin Chen [China West Normal University Nanchong], Zhiyu Xue, Yan Zhang, Zeqin Chen, Ying Xue

J. Mol.Mod.,**22**, 237, 2016.

Levomepromazine, an “older” typical neuroleptic, is widely applied in psychiatry for the treatment of schizophrenia. The biotransformation of Levomepromazine remains elusive up to now, but found to result in the formation of different derivatives that may contribute to the therapeutic and/or side-effects of the parent drug. The present work aims to resolve the metabolic details of Levomepromazine catalyzed by cytochrome P450, an important heme-containing enzyme superfamily, based on DFT calculation.

Putative membrane lytic sites of P-type and S-type cardiotoxins from snake venoms as probed by all-atom molecular dynamics simulations

BiswajitGorai, Muthusamy Karthikeyan, Thirunavukkarasu Sivaraman [SASTRA University Thanjavur]

J. Mol.Mod.,**22**, 238, 2016.

Cardiotoxins (CTXs) belonging to the three-finger toxin superfamily of snake venoms are one of principal toxic components and the protein toxins exhibit membrane lytic activities when the venoms are injected into victims. In the present study, complex formations between CTX VI (a P-type CTX from *Najaatra*) and CTX1 (an S-type CTX from *Najanaja*) on zwitterionic POPC bilayers (a major lipid component of cell membranes) have been studied in near physiological conditions for a total dynamic time scale of 1.35 μ s using all-atom molecular dynamics (MD) simulations.

Theoretical investigation of loratadine reactivity in order to understand its degradation properties: DFT and MD study

StevanArmaković [University of Novi Sad], Sanja J. Armaković, Biljana F. Abramović

J. Mol.Mod.,**22**, 240, 2016.

Antihistamines are frequently used pharmaceuticals that treat the symptoms of allergic reactions. Loratadine (LOR) is an active component of the second generation of selective antihistaminic pharmaceutical usually known as Claritin. Frequent usage of this type of pharmaceuticals imposes the need for understanding their fundamental reactive properties. In this study we have theoretically investigated reactive properties of LOR using both density functional theory (DFT) calculations and molecular dynamics (MD) simulations.

Medicinal Chemistry and Drug Design (Cont'd)

In silico structural characterization of protein targets for drug development against *Trypanosoma cruzi*

Carlyle Ribeiro Lima, Nicolas Carels,
Ana Carolina Ramos Guimaraes, Pierre Tufféry,
Philippe Derreumaux [Instituto Oswaldo Cruz (IOC),
FIOCRUZ]

J. Mol.Mod.,22, 244, 2016.

Trypanosoma cruzi is the protozoan pathogen responsible for Chagas disease, which is a major public health problem in tropical and subtropical regions of developing countries and particularly in Brazil. Despite many studies, there is no efficient treatment against Chagas disease, and the search for new therapeutic targets specific to *T. cruzi* is critical for drug development. Here, we have revisited 41 protein sequences proposed by the analogous enzyme pipeline, and found that it is possible to provide structures for *T. cruzi* sequences.

Computational Discovery and Experimental Confirmation of TLR9 Receptor Antagonist Leads

Maria Zatsepin, Angela Mattes, Steffen Rupp, Doris Finkelmeier, ArijitBasu, Anke Burger-Kentischer, and Amiram Goldblum [The Hebrew University of Jerusalem]

J.Chem. Infor. and Mod., **56**,1835–1846, 2016.

Toll-like receptors (TLR) are receptors of innate immunity that recognize pathogen associated molecular patterns. Immune-modulators are promising molecules for therapeutic intervention in these indications. TLR9 is located in the endosome and activated by dsDNA with CpG motives encountered in microbial DNA. Here we report on a combined approach to discover new TLR9 antagonists by computational chemistry and cell based assays.

Computational Study of Anticancer Drug Resistance Caused by 10 Topoisomerase I Mutations, Including 7 Camptothecin Analogs and Lucanthone

Kelly Mulholland and Chun Wu [Rowan University, Glassboro]

J.Chem. Infor. and Mod., **56**,1872–1883, 2016.

Although Camptothecin and its analogs as Topoisomerase I poisons can effectively treat cancers, serious drug resistance has been identified for this class of drugs. Recent computational studies have indicated that the mutations near the active binding site of the drug can significantly weaken the drug binding and cause drug resistance. However, only Topotecan and three mutations have been previously analyzed. Here we present a comprehensive binding study of 10 Topoisomerase I mutants (N722S, N722A, D533G, D533N, G503S, G717V, T729A, F361S, G363C, and R364H) and 8 poisons including 7 Camptothecin analogs as well as a new generation Topoisomerase I drug, Lucanthone.

Estimation of Liposome Penetration Barriers of Drug Molecules with All-Atom and Coarse-Grained Models

Samuel Genheden [University of Gothenburg] and Leif A. Eriksson

J. Chem. Theor. and Comp, **12**, 4651–4661, 2016.

Liposomes are common carriers of drug molecules, providing enhanced delivery and accumulation of hydrophilic agents or larger biomolecules. Molecular simulations can be used to estimate key features of the drug molecules upon interaction with the liposomes, such as penetration barriers and localization. Herein, we investigate several aspects of the computational estimation of penetration barriers, viz. the potential of mean force (PMFs) along a vector spanning the membrane. First, we provide an evaluation of the all-atom (AA) and coarse-grained (CG) parametrization of 5-aminolevulinic acid (5-ALA) and two of its alkyl esters by computing n-octanol/water partition coefficients.

Medicinal Chemistry and Drug Design (Cont'd)

Pharmacophore-based virtual screening, biological evaluation and binding mode analysis of a novel protease-activated receptor 2 antagonist

Nam-Chul Cho, Seoung-Hwan Seo, Dohee Kim, Ji-Sun Shin, Jeongmin Ju, Jihye Seong, Seon Hee Seo, Iiyoun Lee, Kyung-Tae Lee, Yun Kyung Kim, Kyoung Tai No, Ae Nim Pae[Korea University of Science and Technology, Daejeon]

J.Comp.Aided. Mol.des. **30**, 625-637, 2016.

Protease-activated receptor 2 (PAR₂) is a G protein-coupled receptor, mediating inflammation and pain signaling in neurons, thus it is considered to be a potential therapeutic target for inflammatory diseases. In this study, we performed a ligand-based virtual screening of 1.6 million compounds by employing a common-feature pharmacophore model and two-dimensional similarity search to identify a new PAR₂ antagonist. The common-feature pharmacophore model was established based on the biological screening results of our in-house library.

Mechanism of Inhibition of Cholesteryl Ester Transfer Protein by Small Molecule Inhibitors

Venkat R. Chirasani, RevathiSankar, and SanjibSenapati[Indian Institute of Technology Madras]

J. Phys. Chem. B., **120**, 8254–8263, 2016.

Cholesteryl ester transfer protein (CETP) facilitates the bidirectional exchange of cholesteryl esters and triglycerides between high-density lipoproteins and low- or very low-density lipoproteins. Recent studies have shown that the impairment of lipid exchange processes of CETP can be an effective strategy for the treatment of cardiovascular diseases (CVDs). Understanding the molecular mechanism of CETP inhibition has, therefore, attracted tremendous attention in recent past. In this study, we explored the detailed mechanism of CETP inhibition by a series of recently reported small molecule inhibitors that are currently under preclinical testing.

Molecular Effects of cTnC DCM Mutations on Calcium Sensitivity and Myofilament Activation—An Integrated Multiscale Modeling Study

Sukriti Dewan, Kimberly J. McCabe, Michael Regnier, Andrew D. McCulloch, and Steffen Lindert[Ohio State University, Columbus]

J. Phys. Chem. B., **120**, 8264–8275, 2016.

Mutations in cardiac troponin C (D75Y, E59D, and G159D), a key regulatory protein of myofilament contraction, have been associated with dilated cardiomyopathy (DCM). Despite reports of altered myofilament function in these mutants, the underlying molecular alterations caused by these mutations remain elusive. Here we investigate in silico the intramolecular mechanisms by which these mutations affect myofilament contraction.

Quantitative Structure-Activity Relations

Structure-based approach for the study of thyroid hormone receptor binding affinity and subtype selectivity

Fang-Fang Wang, Wei Yang, Yong-Hui Shi, Xiang-Rong Cheng&Guo-Wei Le [Jiangnan University, Wuxi]

J. Biomol. Stru. andDyn., **34**,2251-2267, 2016.

Thyroid hormone (TH) possesses the ability to lower cholesterol and improve cardiac performance, which have prompted the efforts to design analogs that can utilize the cholesterol-lowering property without adversely affecting heart function. To gain insights into the interaction mechanism for agonists at the active site of thyroid hormone receptor β (TR β), quantitative structure–activity relationship (QSAR) models have been developed on TR β agonists, significant statistical coefficients were obtained (CoMFA, R^2_{cv} , .732), (CoMSIA, R^2_{cv} , .853), indicating the internal consistency of the models, the obtained models were further validated using the test set, the acquired R^2_{pred} values .7054 and .7129 were in good agreement with the experimental results.

QSAR (Cont'd)

Benchmarking the Predictive Power of Ligand Efficiency Indices in QSAR

Isidro Cortes-Ciriano [Institut Pasteur, Unité de Bioinformatique Structurale]

J.Chem. Infor. and Mod., **56**,1576–1587, 2016.

Compound physicochemical properties favoring in vitro potency are not always correlated to desirable pharmacokinetic profiles. Two studies published in this journal showed that higher predictive power on external molecules can be achieved by using ligand efficiency indices as the dependent variable instead of a metric of potency (IC_{50}) or binding affinity (K_i). The present study aims at filling the shortage of a thorough assessment of the predictive power of ligand efficiency indices in QSAR.

Zeolites

Molecular dynamics simulation study: The decryption of bi and tri aromatics behavior with NaX zeolite

M. HaghighiAsl [Ferdowsi University of Mashhad], F. Moosavi, J. Sargolzaei, Kh. Sharifi

J. Mol.Graph. and Mod., **69**,61-71, 2016.

Molecular dynamics simulations have been carried out to provide an atomic description of the behavior of naphthalene and anthracene in NaX zeolite. The force field parameters, which were selected in this process, were chosen carefully to examine dependence of the self-diffusion coefficient of sorbates over a wide range of loading, temperature, and pressure. The simulated adsorption isotherm and calculated adsorption energies at low concentration were found to be in a reasonable qualitative and quantitative agreement with the corresponding scarce experimental data which can evaluate the effectiveness of proposed calculation method and force field parameters.

1.2. Biopolymers

Bioinformatics and Cheminformatics

PRED-TMBB2: improved topology prediction and detection of beta-barrel outer membrane proteins

Konstantinos D. Tsirigos, Arne Elofsson, and Pantelis G. Bagos [University of Thessaly]

Bioinformatics. **32**, i665-i671, 2016.

The PRED-TMBB method is based on Hidden Markov Models and is capable of predicting the topology of beta-barrel outer membrane proteins and discriminate them from water-soluble ones. Here, we present an updated version of the method, PRED-TMBB2, with several newly developed features that improve its performance. The results of a strict cross-validation procedure show that PRED-TMBB2 with homology information performs significantly better compared to other available prediction methods.

Bioinformatics and Cheminformatics (Cont'd)

MOLS 2.0: software package for peptide modeling and protein–ligand docking

D. Sam Paul, N. Gautham [University of Madras, Chennai]

J. Mol.Mod.,**22**, 239, 2016.

We previously developed an algorithm to perform conformational searches of proteins and peptides, and to perform the docking of ligands to protein receptors. In order to identify optimal conformations and docked poses, this algorithm uses mutually orthogonal Latin squares (MOLS) to rationally sample the vast conformational (or docking) space, and then analyzes this relatively small sample using a variant of mean field theory. The conformational search part of the algorithm was denoted MOLS 1.0. The docking portion of the algorithm, which allows only “flexible ligand/rigid receptor” docking, was denoted MOLSDOCK.

PL-PatchSurfer2: Improved Local Surface Matching-Based Virtual Screening Method That Is Tolerant to Target and Ligand Structure Variation

Woong-Hee Shin, Charles W. Christoffer, Jibo Wang, and Daisuke Kihara [Purdue University]

J.Chem. Infor. and Mod., **56**,1676–1691, 2016.

Virtual screening has become an indispensable procedure in drug discovery. Virtual screening methods can be classified into two categories: ligand-based and structure-based. While the former have advantages, including being quick to compute, in general they are relatively weak at discovering novel active compounds because they use known actives as references. Here we report a novel structure-based virtual screening method, PL-PatchSurfer2. In PL-PatchSurfer2, protein and ligand surfaces are represented by a set of overlapping local patches, each of which is represented by three-dimensional Zernike descriptors (3DZDs).

Azahar: a PyMOL plugin for construction, visualization and analysis of glycan molecules

Agustina Arroyuelo, Jorge A. Vila, Osvaldo A. Martin [Universidad Nacional de San Luis and CONICET]

J.Comp.Aided. Mol.des. **30**, 619-624, 2016.

Glycans are key molecules in many physiological and pathological processes. As with other molecules, like proteins, visualization of the 3D structures of glycans adds valuable information for understanding their biological function. Hence, here we introduce Azahar, a computing environment for the creation, visualization and analysis of glycan molecules. Azahar is implemented in Python and works as a plugin for the well known PyMOL package (Schrodinger in The PyMOL molecular graphics system, version 1.3r1, [2010](#)).

Protein Side Chain Confirmation Prediction

Side-Chain Conformational Preferences Govern Protein–Protein Interactions

Andrew M. Watkins, Richard Bonneau, and Paramjit S. Arora
[New York University]

J. Am. Chem. Soc., **138**, 10386–10389, 2016.

Protein secondary structures serve as geometrically constrained scaffolds for the display of key interacting residues at protein interfaces. Given the critical role of secondary structures in protein folding and the dependence of folding propensities on backbone dihedrals, secondary structure is expected to influence the identity of residues that are important for complex formation. Counter to this expectation, we find that a narrow set of residues dominates the binding energy in protein–protein complexes independent of backbone conformation. This finding suggests that the binding epitope may instead be substantially influenced by the side-chain conformations adopted.

Protein Conformational Analysis

A probabilistic model for detecting rigid domains in protein structures

Thach Nguyen and Michael Habeck [University of Göttingen]

Bioinformatics, **32**, i710–i717, 2016.

Large-scale conformational changes in proteins are implicated in many important biological functions. These structural transitions can often be rationalized in terms of relative movements of rigid domains. We present a probabilistic model for detecting rigid-body movements in protein structures. Our model aims to approximate alternative conformational states by a few structural parts that are rigidly transformed under the action of a rotation and a translation.

Building Graphs To Describe Dynamics, Kinetics, and Energetics in the d-ALA:d-Lac Ligase VanA

Nathalie Duclert-Savatier, Guillaume Bouvier, Michael Nilges, and Thérèse E. Malliavin [Institut Pasteur, Unité de Bioinformatique Structurale]

J. Chem. Infor. and Mod., **56**, 1762–1775, 2016.

The d-Ala:d-Lac ligase, VanA, plays a critical role in the resistance of vancomycin. Indeed, it is involved in the synthesis of a peptidoglycan precursor, to which vancomycin cannot bind. The reaction catalyzed by VanA requires the opening of the so-called “ ω -loop”, so that the substrates can enter the active site. Here, the conformational landscape of VanA is explored by an enhanced sampling approach: the temperature-accelerated molecular dynamics (TAMD).

Steered Molecular Dynamics Simulations Predict Conformational Stability of Glutamate Receptors

Maria Musgaard and Philip C. Biggin [University of Oxford, South Parks Road]

J. Chem. Infor. and Mod., **56**, 1787–1797, 2016.

The stability of protein–protein interfaces can be essential for protein function. For ionotropic glutamate receptors, a family of ligand-gated ion channels vital for normal function of the central nervous system, such an interface exists between the extracellular ligand binding domains (LBDs). We illustrate how opening the dimer interface using steered molecular dynamics (SMD) simulations, and analyzing the work values required, provides a quantitative measure for interface stability.

Protein Conformational Analysis (Cont'd)

Can Simulations and Modeling Decipher NMR Data for Conformational Equilibria? Arginine–Vasopressin

Elke Haensele, Nouredin Saleh, Christopher M. Read, Lee Banting, David C. Whitley, and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J.Chem. Infor. and Mod., **56**,1798–1807, 2016.

Arginine vasopressin (AVP) has been suggested by molecular-dynamics (MD) simulations to exist as a mixture of conformations in solution. The ^1H and ^{13}C NMR chemical shifts of AVP in solution have been calculated for this conformational ensemble of ring conformations (identified from a 23 μs molecular-dynamics simulation). The relative free energies of these conformations were calculated using classical metadynamics simulations in explicit water. Chemical shifts for representative conformations were calculated using density-functional theory.

Protein Structure Analysis

UniCon3D: de novo protein structure prediction using united-residue conformational search via stepwise, probabilistic sampling

Debswapna Bhattacharya, Renzhi Cao, and Jianlin Cheng [University of Missouri, Columbia]

Bioinformatics. **32**,2791-2799, 2016.

Recent experimental studies have suggested that proteins fold via stepwise assembly of structural units named ‘foldons’ through the process of sequential stabilization. Here, we develop a novel generative, probabilistic model that simultaneously captures local structural preferences of backbone and side chain conformational space of polypeptide chains in a united-residue representation and performs experimentally motivated conditional conformational sampling via stepwise synthesis and assembly of foldon units that minimizes a composite physics and knowledge-based energy function for de novo protein structure prediction.

Quantification of Compactness and Local Order in the Ensemble of the Intrinsically Disordered Protein FCP1

Eric B. Gibbs and Scott A. Showalter [The Pennsylvania State University]

J. Phys. Chem. B., **120**, 8960–8969, 2016.

Intrinsically disordered protein regions (IDRs) partially or completely lack a cooperatively folded structure under native conditions, preventing their equilibrium state from being adequately described by a single structural model. As a direct consequence of their disorder, remarkably few experimental studies have quantified the ensembles IDRs adopt in solution. Here, we conduct unbiased computer simulations of the RAP74 interaction motif from the human phosphatase FCP1 in the unbound state, which provides an ensemble in quantitative agreement with both experimental NMR chemical shift information and small-angle X-ray scattering data.

Protein Dynamics

Molecular Dynamics Simulations of Amyloid β -Peptide (1-42): Tetramer Formation and Membrane Interactions

Anne M. Brown, David R. Bevan [Virginia Tech, Blacksburg]

Biophysical Journal., **111**, 937-949, 2016.

The aggregation cascade and peptide-membrane interactions of the amyloid β -peptide (A β) have been implicated as toxic events in the development and progression of Alzheimer's disease. A β_{42} forms oligomers and ultimately plaques, and it has been hypothesized that these oligomeric species are the main toxic species contributing to neuronal cell death. To better understand oligomerization events and subsequent oligomer-membrane interactions of A β_{42} , we performed atomistic molecular-dynamics (MD) simulations to characterize both interpeptide interactions and perturbation of model membranes by the peptides.

Evaluation of Methods for the Calculation of the pK_a of Cysteine Residues in Proteins

Ernest Awoonor-Williams and Christopher N. Rowley [Memorial University of Newfoundland]

J. Chem. Theor. and Comp., **12**, 4662–4673, 2016.

Methods for the calculation of the pK_a of ionizable amino acids are valuable tools for understanding pH-dependent properties of proteins. Cysteine is unique among the amino acids because of the chemical reactivity of its thiol group (S–H), which plays an instrumental role in several biochemical and regulatory functions. The pK_a's of these residues were calculated using three methods that use an implicit solvent model (H++, MCCE, and PROPKA) and an all-atom replica-exchange thermodynamic integration approach with the CHARMM36 and AMBER ff99SB-ILDNP force fields.

Osmotic Pressure Simulations of Amino Acids and Peptides Highlight Potential Routes to Protein Force Field Parameterization

Mark S. Miller, Wesley K. Lay, and Adrian H. Elcock [University of Iowa, Iowa City]

J. Phys. Chem. B., **120**, 8217–8229, 2016.

Recent molecular dynamics (MD) simulations of proteins have suggested that common force fields overestimate the strength of amino acid interactions in aqueous solution. In an attempt to determine the causes of these effects, we have measured the osmotic coefficients of a number of amino acids using the AMBER ff99SB-ILDN force field with two popular water models, and compared the results with available experimental data. With TIP4P-Ew water, interactions between aliphatic residues agree well with experiment, but interactions of the polar residues serine and threonine are found to be excessively attractive.

Identification of an Electrostatic Ruler Motif for Sequence-Specific Binding of Collagenase to Collagen

Sundar Raman Subramanian, Ettayapuram Ramaprasad Azhagiya Singam, Michael Berinski, Venkatesan Subramanian, and Rebecca C. Wade [Heidelberg Institute for Theoretical Studies]

J. Phys. Chem. B., **120**, 8580–8589, 2016.

Sequence-specific cleavage of collagen by mammalian collagenase plays a pivotal role in cell function. Collagenases are matrix metalloproteinases that cleave the peptide bond at a specific position on fibrillar collagen. The collagenase Hemopexin-like (HPX) domain has been proposed to be responsible for substrate recognition, but the mechanism by which collagenases identify the cleavage site on fibrillar collagen is not clearly understood. In this study, Brownian dynamics simulations coupled with atomic-detail and coarse-grained molecular dynamics simulations were performed to dock matrix metalloproteinase-1 (MMP-1) on a collagen III α 1 triple helical peptide.

Protein Dynamics (Cont'd)

Structure and Dynamics of Extracellular Loops in Human Aquaporin-1 from Solid-State NMR and Molecular Dynamics

Shenlin Wang, Christopher Ing, Sanaz Emami, Yunjiang Jiang, Hongjun Liang, Régis Pomès, Leonid S. Brown, and Vladimir Ladizhansky [University of Guelph]

J. Phys. Chem. B., **120**, 9887–9902, 2016.

Multiple moderate-resolution crystal structures of human aquaporin-1 have provided a foundation for understanding the molecular mechanism of selective water translocation in human cells. To gain insight into the interfacial structure and dynamics of human aquaporin-1 in a lipid environment, we performed nuclear magnetic resonance (NMR) spectroscopy and molecular dynamics simulations. Using magic angle spinning solid-state NMR, we report a near complete resonance assignment of the human aquaporin-1.

Characterization of the flexibility of the peripheral stalk of prokaryotic rotary A-ATPases by atomistic simulations

Kostas Papachristos, Stephen P. Muench and Emanuele Paci [University of Leeds, Leeds]

Proteins: Stru. Fun. & Bioinf., **84**, 1203–1212, 2016.

Rotary ATPases are involved in numerous physiological processes, with the three distinct types (F/A/V-ATPases) sharing functional properties and structural features. The basic mechanism involves the counter rotation of two motors, a soluble ATP hydrolyzing/synthesizing domain and a membrane-embedded ion pump connected through a central rotor axle and a stator complex. Here we use long, detailed atomistic simulations to show that those structures are conformers explored through thermal fluctuations, but do not represent highly populated states of the EG stator in solution.

Free Energy Calculations

Sensitivity in Binding Free Energies Due to Protein Reorganization

Nathan M. Lim, Lingle Wang, Robert Abel, and David L. Mobley [Chemistry University of California—Irvine]

J. Chem. Theor. and Comp., **12**, 4620–4631, 2016.

Tremendous recent improvements in computer hardware, coupled with advances in sampling techniques and force fields, are now allowing protein–ligand binding free energy calculations to be routinely used to aid pharmaceutical drug discovery projects. However, despite these recent innovations, there are still needs for further improvement in sampling algorithms to more adequately sample protein motion relevant to protein–ligand binding. Here, we report our work identifying and studying such clear and remaining needs in the apolar cavity of T4 lysozyme L99A.

Free Energy Landscape of Lipid Interactions with Regulatory Binding Sites on the Transmembrane Domain of the EGF Receptor

George Hedger, David Shorthouse, Heidi Koldsø, and Mark S. P. Sansom [University of Oxford, South Parks Road]

J. Phys. Chem. B., **120**, 8154–8163, 2016.

Lipid molecules can bind to specific sites on integral membrane proteins, modulating their structure and function. We have undertaken coarse-grained simulations to calculate free energy profiles for glycolipids and phospholipids interacting with modulatory sites on the transmembrane helix dimer of the EGF receptor within a lipid bilayer environment. We identify lipid interaction sites at each end of the transmembrane domain and compute interaction free energy profiles for lipids with these sites.

Free Energy Calculations (Cont'd)

Mechanism of pKID/KIX Association Studied by Molecular Dynamics Free Energy Simulations

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[Technische Universität München]

J. Phys. Chem. B., **120**, 8186–8192, 2016.

The phosphorylated kinase-inducible domain (pKID) associates with the kinase interacting domain (KIX) via a coupled folding and binding mechanism. The pKID domain is intrinsically disordered when unbound and upon phosphorylation at Ser133 binds to the KIX domain adopting a well-defined kinked two-helix structure. In order to identify putative hot spot residues of binding that could serve as an initial stable anchor, we performed in silico alanine scanning free energy simulations.

A Simple and Accurate Method To Calculate Free Energy Profiles and Reaction Rates from Restrained Molecular Simulations of Diffusive Processes

Victor Ovchinnikov, Kwangho Nam, and Martin Karplus [Harvard University, Cambridge]

J. Phys. Chem. B., **120**, 8457–8472, 2016.

A method is developed to obtain simultaneously free energy profiles and diffusion constants from restrained molecular simulations in diffusive systems. The method is based on low-order expansions of the free energy and diffusivity as functions of the reaction coordinate. These expansions lead to simple analytical relationships between simulation statistics and model parameters. The method is tested on 1D and 2D model systems; its accuracy is found to be comparable to or better than that of the existing alternatives, which are briefly discussed.

Ligand Binding/Docking

Exploring dual inhibitors for STAT1 and STAT5 receptors utilizing virtual screening and dynamics simulation validation

Utkarsh Raj, Himansu Kumar, Saurabh Gupta & Pritish Kumar Varadwaj [Indian Institute of Information Technology – Allahabad]

J. Biomol. Stru. And Dyn., **34**, 2115–2129, 2016.

Signal transducer and activator of transcription (STAT) proteins are latent cytoplasmic transcription factors that transduce signals from cytokines and growth factors to the nucleus and thereby regulate the expression of a variety of target genes. The purpose of this study is to identify domain-specific dual inhibitors for both STAT1 and STAT5 proteins from a database of natural products and natural product-like compounds comprising of over 90,000 compounds.

Structure–Activity Relationship and Signaling of New Chimeric CXCR4 Agonists

Christine E. Mona, Élie Besserer-Offroy, Jérôme Cabana, Marilou Lefrançois, Philip E. Boulais, Marie-Reine Lefebvre, Richard Leduc, Pierre Lavigne, Nikolaus Heveker, Éric Marsault, and Emanuel Escher [Université de Sherbrooke, Sherbrooke]

Jou. Med. Chem., **59**, 7512–7524, 2016.

The CXCR4 receptor binds with meaningful affinities only CXCL12 and synthetic antagonists/inverse agonists. We recently described high affinity synthetic agonists for this chemokine receptor, obtained by grafting the CXCL12 N-terminus onto the inverse agonist T140. While those chimeric molecules behave as agonists for CXCR4, their binding and activation mode are unknown. The present SAR of those CXCL12-oligopeptide grafts reveals the key determinants involved in CXCR4 activation. Position 3 (Val) controls affinity, whereas position 7 (Tyr) acts as an efficacy switch.

Ligand Binding / Docking (Cont'd)

Apo- and Antagonist-Binding Structures of Vitamin D Receptor Ligand-Binding Domain Revealed by Hybrid Approach Combining Small-Angle X-ray Scattering and Molecular Dynamics

Yasuaki Anami, Nobutaka Shimizu, Toru Ekimoto, Daichi Egawa, Toshimasa Itoh, Mitsunori Ikeguchi, and Keiko Yamamoto [Showa Pharmaceutical University]

Jou. Med. Chem., 59, 7888–7900, 2016.

Vitamin D receptor (VDR) controls the expression of numerous genes through the conformational change caused by binding 1 α ,25-dihydroxyvitamin D₃. Helix 12 in the ligand-binding domain (LBD) is key to regulating VDR activation. The structures of apo VDR-LBD and the VDR-LBD/antagonist complex are unclear. Here, we reveal their unprecedented structures in solution using a hybrid method combining small-angle X-ray scattering and molecular dynamics simulations.

Simulations reveal increased fluctuations in estrogen receptor- α conformation upon antagonist binding

Ho Leung Ng [University of Hawaii Cancer Center]

J. Mol. Graph. and Mod., 69, 72–77, 2016.

Molecular dynamics (MD) simulations have been used to model dynamic fluctuations in the structure of estrogen receptor- α (ER- α) upon binding to the natural agonist 17 β -estradiol (E2) and to the active metabolite of the breast cancer drug and antagonist, 4-hydroxytamoxifen (OHT). We present the most extensive MD simulations to date of ER- α , with over 1 μ s of combined simulations for the monomer and dimer forms. Simulations reveal that the antagonist-bound complex includes significant fluctuations while the agonist-bound complex is tightly restrained.

Probing Allosteric Inhibition Mechanisms of the Hsp70 Chaperone Proteins Using Molecular Dynamics Simulations and Analysis of the Residue Interaction Networks

Gabrielle Stetz and Gennady M. Verkhivker [Schmid College of Science and Technology]

J. Chem. Infor. and Mod., 56, 1490–1517, 2016.

Although molecular mechanisms of allosteric regulation in the Hsp70 chaperones have been extensively studied at both structural and functional levels, the current understanding of allosteric inhibition of chaperone activities by small molecules is still lacking. In the current study, using a battery of computational approaches, we probed allosteric inhibition mechanisms of E. coli Hsp70 (DnaK) and human Hsp70 proteins by small molecule inhibitors PET-16 and novolactone. Molecular dynamics simulations and binding free energy analysis were combined with network-based modeling of residue interactions and allosteric communications.

Selective Inhibition of STAT3 with Respect to STAT1: Insights from Molecular Dynamics and Ensemble Docking Simulations

Semen O. Yesylevskyy [National Academy of Sciences of Ukraine], Christophe Ramseyer, Marc Pudlo, Jean-René Pallandre, and Christophe Borg

J. Chem. Infor. and Mod., 56, 1588–1596, 2016.

STAT3 protein, which is known to be involved in cancer development, is a promising target for anticancer therapy. Successful inhibitors of STAT3 should not affect an activity of closely related protein STAT1, which makes their development challenging. The mechanisms of selectivity of several existing STAT3 inhibitors are not clear. In this work, we studied molecular mechanisms of selectivity of 13 experimentally tested STAT3 inhibitors by means of extensive molecular dynamics and ensemble docking simulations.

Ligand Binding / Docking (Cont'd)

Motions of Allosteric and Orthosteric Ligand-Binding Sites in Proteins are Highly Correlated

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J.Chem. Infor. and Mod., **56**,1725–1733, 2016.

Allostery is the phenomenon in which a ligand binding at one site affects other sites in the same macromolecule. Allostery has important roles in many biological processes. Theoretically, all nonfibrous proteins are potentially allosteric. However, few allosteric proteins have been validated, and the identification of novel allosteric sites remains a challenge. We utilized a data set of 24 known allosteric sites from 23 monomer proteins to calculate the correlations between potential ligand-binding sites and corresponding orthosteric sites using a Gaussian network model (GNM).

Structural Diversity of Ligand-Binding Androgen Receptors Revealed by Microsecond Long Molecular Dynamics Simulations and Enhanced Sampling

MojieDuan, Na Liu, Wenfang Zhou, Dan Li, Minghui Yang, and TingjunHou [Zhejiang University, Hangzhou]

J. Chem. Theor. and Comp, **12**, 4611–4619, 2016.

Androgen receptor (AR) plays important roles in the development of prostate cancer (PCa). The antagonistic drugs, which suppress the activity of AR, are widely used in the treatment of PCa. However, the molecular mechanism of antagonism about how ligands affect the structures of AR remains elusive. To better understand the conformational variability of ARs bound with agonists or antagonists, we performed long time unbiased molecular dynamics (MD) simulations and enhanced sampling simulations for the ligand binding domain of AR (AR-LBD) in complex with various ligands.

Solvent Fluctuations Induce Non-Markovian Kinetics in Hydrophobic Pocket-Ligand Binding

R. GregorWeiß, Piotr Setny, and Joachim Dzubiella[Humboldt-Universität zu Berlin]

J. Phys. Chem. B., **120**, 8127–8136, 2016.

We investigate the impact of water fluctuations on the key-lock association kinetics of a hydrophobic ligand (key) binding to a hydrophobic pocket (lock) by means of a minimalistic stochastic model system. The latter describes the collective hydration behavior of the pocket by bimodal fluctuations of the water-pocket interface that dynamically couples to the diffusive motion of the approaching ligand via the hydrophobic interaction.

Recognition of Poly-Ubiquitins by the Proteasome through Protein Refolding Guided by Electrostatic and Hydrophobic Interactions

Yi Zhang, Lela Vuković, Till Rudack, Wei Han, and Klaus Schulten[University of Illinois at Urbana-Champaign]

J. Phys. Chem. B., **120**, 8137–8146, 2016.

Specificity of protein degradation by cellular proteasomes comes from tetra-ubiquitin recognition. We carry out molecular dynamics simulations to characterize how the ubiquitin receptor Rpn10 recognizes in the 26S proteasome K48-linked tetra-ubiquitin. In the binding pose, ubiquitin and Rpn10 interact primarily through hydrophobic patches. However, K48-linked tetra-ubiquitin mostly assumes a closed form in solution prior to binding, in which its hydrophobic patches are not exposed to solvent.

Ligand Binding / Docking (Cont'd)

Coupled Dynamics and Entropic Contribution to the Allosteric Mechanism of Pin1

Arghya Barman and Donald Hamelberg [Georgia State University, Atlanta]

J. Phys. Chem. B., **120**, 8405–8415, 2016.

Allosteric communication in proteins regulates a plethora of downstream processes in subcellular signaling pathways. Describing the effects of cooperative ligand binding on the atomic level is a key to understanding many regulatory processes involving biomolecules. Here, we use microsecond-long molecular dynamics simulations to investigate the allosteric mechanism of Pin1, a potential therapeutic target and a phosphorylated-Ser/Thr dependent peptidyl-prolyl cis-trans isomerase that regulates several subcellular processes and has been implicated in many diseases, including cancer and Alzheimer's.

Analysis of Ligand-Receptor Association and Intermediate Transfer Rates in Multienzyme Nanostructures with All-Atom Brownian Dynamics Simulations

Christopher C. Roberts and Chia-en A. Chang [University of California, Riverside]

J. Phys. Chem. B., **120**, 8518–8531, 2016.

We present the second-generation GeomBD Brownian dynamics software for determining interenzyme intermediate transfer rates and substrate association rates in biomolecular complexes. Substrate and intermediate association rates for a series of enzymes or biomolecules can be compared between the freely diffusing disorganized configuration and various colocalized or complexed arrangements for kinetic investigation of enhanced intermediate transfer. In addition, enzyme engineering techniques, such as synthetic protein conjugation, can be computationally modeled and analyzed to better understand changes in substrate association relative to native enzymes.

Understanding Ion Binding Affinity and Selectivity in β -Parvalbumin Using Molecular Dynamics and Mean Spherical Approximation Theory

Amir N. Kucharski, Caitlin E. Scott [University of Kentucky, Lexington], Jonathan P. Davis, and Peter M. Keken-Huskey

J. Phys. Chem. B., **120**, 8617–8630, 2016.

Parvalbumin (PV) is a globular calcium (Ca^{2+})-selective protein expressed in a variety of biological tissues. Our computational studies of the rat β -parvalbumin (β -PV) isoform seek to elucidate the molecular thermodynamics of Ca^{2+} versus magnesium (Mg^{2+}) binding at the protein's two EF-hand motifs. Specifically, we have utilized molecular dynamics (MD) simulations and a mean-field electrolyte model (mean spherical approximation (MSA) theory) to delineate how the EF-hand scaffold controls the "local" thermodynamics of Ca^{2+} binding selectivity over Mg^{2+} .

Enzyme Catalysis

Molecular basis of the recognition of FMN by a HAD phosphatase TON_0338

Rui-Juan Niu, Qing-Chuan Zheng [Jilin University, Changchun], Hong-Xing Zhang

J. Mol. Graph. and Mod., **69**,17-25, 2016.

The haloalkaloic acid dehalogenase (HAD) phosphatase from *Thermococcus onnurineus* NA1 (TON_0338), has phosphatase activity the flavin mono-nucleotide (FMN). The molecular origin and structural motifs for the activity deficiency of double-tryptophan mutant have not been rationalized at atomic resolution. Molecular dynamics (MD) simulations and the molecular mechanics/Generalized-Born surface area (MM/GBSA) free energy calculations were used to explore the effects of mutations on the changes in both structural flexibility and conformational dynamics.

Exploring ligand dissociation pathways from aminopeptidase N using random acceleration molecular dynamics simulation

Ya Liu, GuoGangTu [NanChang University], XiaoPing Lai, BinHaiKuang, ShaoHua Li

J. Mol. Mod., **22**, 236, 2016.

Aminopeptidase N (APN) is a zinc-dependent ectopeptidase involved in cell proliferation, secretion, invasion, and angiogenesis, and is widely recognized as an important cancer target. However, the mechanisms whereby ligands leave the active site of APN remain unknown. Investigating ligand dissociation processes is quite difficult, both in classical simulation methods and in experimental approaches. In this study, random acceleration molecular dynamics (RAMD) simulation was used to investigate the potential dissociation pathways of ligand from APN.

Product Release Pathways in Human and Plasmodium falciparum Phosphoribosyltransferase

TarakKarmakar, Sourav Roy, HemalathaBalaram, Meher K. Prakash, and SundaramBalasubramanian [Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore]

J. Chem. Infor. and Mod., **56**,1528–1538, 2016.

Atomistic molecular dynamics (MD) simulations coupled with the metadynamics technique were carried out to delineate the product (PPi.2Mg and IMP) release mechanisms from the active site of both human (Hs) and *Plasmodium falciparum* (Pf) hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT). An early movement of PPi.2Mg from its binding site has been observed. The swinging motion of the Asp side chain (D134/D145) in the binding pocket facilitates the detachment of IMP, which triggers the opening of flexible loop II, the gateway to the bulk solvent.

Unprecedentedly Large-Scale Kinase Inhibitor Set Enabling the Accurate Prediction of Compound–Kinase Activities: A Way toward Selective Promiscuity by Design?

Serge Christmann-Franck [Merck Serono, Chemin des Mines 9], Gerard J. P. van Westen, George Papadatos, Fanny Beltran Escudie, Alexander Roberts, John P. Overington, and Daniel Domine

J. Chem. Infor. and Mod., **56**,1654–1675, 2016.

Drug discovery programs frequently target members of the human kinome and try to identify small molecule protein kinase inhibitors, primarily for cancer treatment, additional indications being increasingly investigated. One of the challenges is controlling the inhibitors degree of selectivity, assessed by in vitro profiling against panels of protein kinases. We manually extracted, compiled, and standardized such profiles published in the literature: we collected 356 908 data points corresponding to 482 protein kinases, 2106 inhibitors, and 661 patents.

Enzyme Catalysis (Cont'd)

Understanding the Catalytic Mechanism of Xanthosine Methyltransferase in Caffeine Biosynthesis from QM/MM Molecular Dynamics and Free Energy Simulations

Ping Qian, Hao-Bo Guo, Yufei Yue, Liang Wang, Xiaohan Yang, and Hong Guo [University of Tennessee, Knoxville]

J.Chem. Infor. and Mod., **56**,1755–1761, 2016.

S-Adenosyl-l-methionine (SAM) dependent xanthosine methyltransferase (XMT) is the key enzyme that catalyzes the first methyl transfer in the caffeine biosynthesis pathway to produce the intermediate 7-methylxanthosine (7mXR). Although XMT has been a subject of extensive discussions, the catalytic mechanism and nature of the substrate involved in the catalysis are still unclear. In this paper, quantum mechanical/molecular mechanical (QM/MM) molecular dynamics (MD) and free energy (potential of mean force or PMF) simulations are undertaken to determine the catalytic mechanism of the XMT-catalyzed reaction.

Secondary Interaction Interfaces with PCNA Control Conformational Switching of DNA Polymerase PolB from Polymerization to Editing

Xiaojun Xu, Chunli Yan, Bradley R. Kossman, and Ivaylo Ivanov [Georgia State University, Atlanta]

J. Phys. Chem. B., **120**, 8379–8388, 2016.

Replicative DNA polymerases (Pols) frequently possess two distinct DNA processing activities: DNA synthesis (polymerization) and proofreading (3'–5' exonuclease activity). The polymerase and exonuclease reactions are performed alternately and are spatially separated in different protein domains. The mechanism of this conformational switching and the role that PCNA plays in it have remained obscure, largely due to the dynamic nature of ternary Pol/PCNA/DNA assemblies. Here, we present computational models of ternary assemblies for archaeal polymerase PolB.

Protein-Protein Interactions

ModuleAlign: module-based global alignment of protein–protein interaction networks

SomayeHashemifar, Jianzhu Ma, Hammad Naveed, Stefan Canzar [Toyota Technological Institute at Chicago], and Jinbo Xu

Bioinformatics. **32**, i658–i664, 2016.

As an increasing amount of protein–protein interaction (PPI) data becomes available, their computational interpretation has become an important problem in bioinformatics. In this work, we present a novel global network alignment algorithm, named ModuleAlign, which makes use of local topology information to define a module-based homology score. Based on a hierarchical clustering of functionally coherent proteins involved in the same module, ModuleAlign employs a novel iterative scheme to find the alignment between two networks.

PEPSI-Dock: a detailed data-driven protein–protein interaction potential accelerated by polar Fourier correlation

Emilie Neveu, David W. Ritchie, Petr Popov, and Sergei Grudinin [Inria/University Grenoble Alpes/LJK-CNRS]

Bioinformatics. **32**, i693–i701, 2016.

Docking prediction algorithms aim to find the native conformation of a complex of proteins from knowledge of their unbound structures. They rely on a combination of sampling and scoring methods, adapted to different scales. Polynomial Expansion of Protein Structures and Interactions for Docking (PEPSI-Dock) improves the accuracy of the first stage of the docking pipeline, which will sharpen up the final predictions. We present a process to compute data-driven distant-dependent pairwise potentials, adapted from our previous method for rescoring of putative protein–protein binding poses.

Protein - Protein Interactions (Cont'd)

Improved Computation of Protein–Protein Relative Binding Energies with the Nwat-MMGBSA Method

Irene Maffucci and Alessandro Contini [Università degli Studi di Milano]

J.Chem. Infor. and Mod., **56**,1692–1704, 2016.

A MMGBSA variant (here referred to as Nwat-MMGBSA), based on the inclusion of a certain number of explicit water molecules (Nwat) during the calculations, has been tested on a set of 20 protein–protein complexes, using the correlation between predicted and experimental binding energy as the evaluation metric. Besides the Nwat parameter, the effect of the force field, the molecular dynamics simulation length, and the implicit solvent model used in the MMGBSA analysis have been also evaluated.

Multi-Conformation Monte Carlo: A Method for Introducing Flexibility in Efficient Simulations of Many-Protein Systems

Vera Prytkova, Matthias Heyden, Domarin Khago, J. Alfredo Freites, Carter T. Butts, Rachel W. Martin, and Douglas J. Tobias [University of California, Irvine]

J. Phys. Chem. B., **120**, 8115–8126, 2016.

We present a novel multi-conformation Monte Carlo simulation method that enables the modeling of protein–protein interactions and aggregation in crowded protein solutions. This approach is relevant to a molecular-scale description of realistic biological environments, including the cytoplasm and the extracellular matrix, which are characterized by high concentrations of biomolecular solutes (e.g., 300–400 mg/mL for proteins and nucleic acids in the cytoplasm of *Escherichia coli*). Simulation of such environments necessitates the inclusion of a large number of protein molecules.

Protein–protein structure prediction by scoring molecular dynamics trajectories of putative poses

Edoardo Sarti, Ivan Gladich, Stefano Zamuner, Bruno E. Correia and Alessandro Laio [SISSA, via Bonomea 265]

Proteins: Stru. Fun. & Bioinf., **84**, 1312–1320, 2016.

The prediction of protein–protein interactions and their structural configuration remains a largely unsolved problem. Most of the algorithms aimed at finding the native conformation of a protein complex starting from the structure of its monomers are based on searching the structure corresponding to the global minimum of a suitable scoring function. We here benchmark the capability of some state-of-the-art scoring functions (BACH-SixthSense, PIE/PISA and Rosetta) in discriminating finite-temperature ensembles of structures corresponding to the native state and to non-native configurations.

Membrane Proteins and Lipid Peptide Interactions

Calculating protein–ligand binding affinities with MMPBSA: Method and error analysis

Changhao Wang, Peter H. Nguyen, Kevin Pham, Danielle Huynh, Thanh-Binh Nancy Le, Hongli Wang, Pengyu Ren and Ray Luo [Chemical and Materials Physics Graduate Program, Irvine]

J. Comp. Chem., **37**, 2436–2446, 2016.

Molecular Mechanics Poisson–Boltzmann Surface Area (MMPBSA) methods have become widely adopted in estimating protein–ligand binding affinities due to their efficiency and high correlation with experiment. Here different computational alternatives were investigated to assess their impact to the agreement of MMPBSA calculations with experiment. Seven receptor families with both high-quality crystal structures and binding affinities were selected. First the performance of nonpolar solvation models was studied and it was found that the modern approach that separately models hydrophobic and dispersion interactions dramatically reduces RMSD's of computed relative binding affinities.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Antimicrobial Peptide Simulations and the Influence of Force Field on the Free Energy for Pore Formation in Lipid Bilayers

W. F. Drew Bennett, Chun Kit Hong, Yi Wang, and D. Peter Tieleman [University of Calgary, Calgary]

J. Chem. Theor. and Comp, **12**, 4524–4533, 2016.

Due to antimicrobial resistance, the development of new drugs to combat bacterial and fungal infections is an important area of research. Nature uses short, charged, and amphipathic peptides for antimicrobial defense, many of which disrupt the lipid membrane in addition to other possible targets inside the cell. Here, we performed microsecond-long simulations of the antimicrobial peptide CM15 in a POPC bilayer expecting to observe pore formation (based on previous molecular dynamics simulations).

Dissecting the Influence of Protein Flexibility on the Location and Thermodynamic Profile of Explicit Water Molecules in Protein–Ligand Binding

Ying Yang and Markus A. Lill [College of Pharmacy, Purdue University]

J. Chem. Theor. and Comp, **12**, 4578–4592, 2016.

Explicit water molecules in the binding site of proteins play a crucial role for protein–ligand association. Recent advances in computer-aided drug discovery methodology allow for an accurate prediction of the localized position and thermodynamic profile of water molecules (i.e., hydration sites) in the binding site. In this manuscript, we present the developments of two methods to incorporate the influence of protein conformational change on hydration sites either by following the conformational transition step-by-step (method I) or to match the hydration sites of the two transition end states using local coordinate systems (method II).

Markovian and Non-Markovian Modeling of Membrane Dynamics with Milestoning

Alfredo E. Cardenas and Ron Elber [University of Texas at Austin]

J. Phys. Chem. B., **120**, 8208–8216, 2016.

We exploit atomically detailed simulations and the milestoning theory to extract coarse grained models of membrane kinetics and thermodynamics. Non-Markovian and Markovian theories for the phosphate group displacements are used to coarsely represent membrane motions. The construction of the two models makes it possible to examine their consistency and accuracy. The equilibrium and fluctuations of the phosphate groups along the normal to the membrane plane are estimated, and milestoning equations are constructed and solved.

Ionic Hydrogen Bonds and Lipid Packing Defects Determine the Binding Orientation and Insertion Depth of RecA on Multicomponent Lipid Bilayers

Leili Zhang, Manohary Rajendram, Douglas B. Weibel, Arun Yethiraj, and Qiang Cui [University of Wisconsin—Madison]

J. Phys. Chem. B., **120**, 8424–8437, 2016.

We describe a computational and experimental approach for probing the binding properties of the RecA protein at the surface of anionic membranes. Fluorescence measurements indicate that RecA behaves differently when bound to phosphatidylglycerol (PG)- and cardiolipin (CL)-containing liposomes. We use a multistage computational protocol that integrates an implicit membrane/solvent model, the highly mobile mimetic membrane model, and the full atomistic membrane model to study how different anionic lipids perturb RecA binding to the membrane.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Behavior of Bilayer Leaflets in Asymmetric Model Membranes: Atomistic Simulation Studies

Jianhui Tian, Jonathan Nickels, John Katsaras, and Xiaolin Cheng [Oak Ridge National Laboratory]

J. Phys. Chem. B., **120**, 8438–8448, 2016.

Spatial organization within lipid bilayers is an important feature for a range of biological processes. Leaflet compositional asymmetry and lateral lipid organization are just two of the ways in which membrane structure appears to be more complex than initially postulated by the fluid mosaic model. Here we report on all-atom molecular dynamics simulations (a total of 4.1 μ s) of symmetric and asymmetric bilayer systems composed of liquid-ordered (Lo) or liquid-disordered (Ld) leaflets, based on the nanodomain-forming POPC/DSPC/cholesterol system.

Behavior of P85 and P188 Poloxamer Molecules: Computer Simulations Using United-Atom Force-Field

ArdeshtirGolizadeh, Edmond Y. Lau, UpendraAdhikari, Eric Schwegler, and Max L. Berkowitz [University of North Carolina at Chapel Hill]

J. Phys. Chem. B., **120**, 8631–8641, 2016.

To study the interaction between poloxamer molecules and lipid bilayers using molecular dynamics simulation technique with the united-atom resolution, we augmented the GROMOS force-field to include poloxamers. We validated the force-field by calculating the radii of gyration of two poloxamers, P85 and P188, solvated in water and by considering the poloxamer density distributions at the air/water interface.

Membrane Compartmentalization Reducing the Mobility of Lipids and Proteins within a Model Plasma Membrane

Heidi Koldsø, Tyler Reddy, Philip W. Fowler, Anna L. Duncan, and Mark S. P. Sansom [University of Oxford, South Parks Road]

J. Phys. Chem. B., **120**, 8873–8881, 2016.

The cytoskeleton underlying cell membranes may influence the dynamic organization of proteins and lipids within the bilayer by immobilizing certain transmembrane (TM) proteins and forming corrals within the membrane. Here, we present coarse-grained resolution simulations of a biologically realistic membrane model of asymmetrically organized lipids and TM proteins. We determine the effects of a model of cytoskeletal immobilization of selected membrane proteins using long time scale coarse-grained molecular dynamics simulations.

Molecular Dynamics Simulation Study of Permeation of Molecules through Skin Lipid Bilayer

Rakesh Gupta, D. B. Sridhar, and Beena Rai [Tata Research Development and Design Centre]

J. Phys. Chem. B., **120**, 8987–8996, 2016.

Stratum Corneum (SC), the outermost layer of skin, is mainly responsible for skin's barrier function. The complex lipid matrix of SC determines these barrier properties. In this study, the lipid matrix is modeled as an equimolar mixture of ceramide (CER), cholesterol (CHOL), and free fatty acid (FFA). The permeation of water, oxygen, ethanol, acetic acid, urea, butanol, benzene, dimethyl sulfoxide (DMSO), toluene, phenol, styrene, and ethylbenzene across this layer is studied using a constrained MD simulations technique.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

A Coarse-Grained Model of Stratum Corneum Lipids: Free Fatty Acids and Ceramide NS

Timothy C. Moore, Christopher R. Iacovella, Remco Hartkamp, Annette L. Bunge, and Clare McCabe [Vanderbilt University, Nashville]

J. Phys. Chem. B., **120**, 9944–9958, 2016.

Ceramide (CER)-based biological membranes are used both experimentally and in simulations as simplified model systems of the skin barrier. Molecular dynamics studies have generally focused on simulating preassembled structures using atomistically detailed models of CERs, which limit the system sizes and time scales that can practically be probed, rendering them ineffective for studying particular phenomena, including self-assembly into bilayer and lamellar superstructures. Here, we report on the development of a coarse-grained (CG) model for CER NS, the most abundant CER in human stratum corneum.

Protein Folding

Computer Folding of RNA Tetraloops: Identification of Key Force Field Deficiencies

Petra Kührová, Robert B. Best, Sandro Bottaro, Giovanni Bussi, Jiří Šponer [Palacky University Olomouc], Michal Otyepka, and Pavel Banáš

J. Chem. Theor. and Comp., **12**, 4534–4548, 2016.

The computer-aided folding of biomolecules, particularly RNAs, is one of the most difficult challenges in computational structural biology. RNA tetraloops are fundamental RNA motifs playing key roles in RNA folding and RNA–RNA and RNA–protein interactions. Although state-of-the-art Molecular Dynamics (MD) force fields correctly describe the native state of these tetraloops as a stable free-energy basin on the microsecond time scale, enhanced sampling techniques reveal that the native state is not the global free energy minimum, suggesting yet unidentified significant imbalances in the force fields.

Folding PDZ2 Domain Using the Molecular Transfer Model

Zhenxing Liu [Beijing Normal University], Govardhan Reddy, and D. Thirumalai

J. Phys. Chem. B., **120**, 8090–8101, 2016.

A major challenge in molecular simulations is to describe denaturant-dependent folding of proteins in order to make direct comparisons with in vitro experiments. We use the molecular transfer model (MTM), currently the only method that accomplishes this goal, albeit phenomenologically, to quantitatively describe urea-dependent folding of the PDZ2 domain, a protein that is important in molecular recognition and signaling.

Folding Mechanism of Proteins Im7 and Im9: Insight from All-Atom Simulations in Implicit and Explicit Solvent

F. Wang, G. Cazzolli, P. Wintrod, and P. Faccioli [University of Trento]

J. Phys. Chem. B., **120**, 9297–9307, 2016.

Im7 and Im9 are evolutionary related proteins with almost identical native structures. In spite of their structural similarity, experiments show that Im7 folds through a long-lived on-pathway intermediate, while Im9 folds according to two-state kinetics. In this work, we use a recently developed enhanced path sampling method to generate many folding trajectories for these proteins, using realistic atomistic force fields, in both implicit and explicit solvent. Overall, our results are in good agreement with the experimental ϕ values and with the result of ϕ -value-restrained molecular dynamics (MD) simulations.

Protein-Nucleic acid Interactions

Adding energy minimization strategy to peptide-design algorithm enables better search for RNA-binding peptides: Redesigned λ N peptide binds boxB RNA

Xingqing Xiao, Michelle E. Hung, Joshua N. Leonard and Carol K. Hall [North Carolina State University, Raleigh]

J. Comp. Chem., **37**, 2423–2435, 2016.

Our previously developed peptide-design algorithm was improved by adding an energy minimization strategy which allows the amino acid sidechains to move in a broad configuration space during sequence evolution. In this work, the new algorithm was used to generate a library of 21-mer peptides which could substitute for λ N peptide in binding to *boxB* RNA. Six potential peptides were obtained from the algorithm, all of which exhibited good binding capability with *boxB* RNA.

Estimation of Relative Protein–RNA Binding Strengths from Fluctuations in the Bound State

ZhalehGhaemi, Irisbel Guzman, Jung-un Julia Baek, Martin Gruebele, and ZaidaLuthey-Schulten [University of Illinois at Urbana–Champaign]

J. Chem. Theor. and Comp., **12**, 4593–4599, 2016.

Protein–RNA complexes are increasingly important in our understanding of cell signaling, metabolism, and transcription. Electrostatic interactions play dominant role in stabilizing such complexes. Using conventional computational approaches, very long simulations of both bound and unbound states are required to obtain accurate estimates of complex dissociation constants (K_d). Here, we derive a simple formula that offers an alternative approach based on the theory of fluctuations.

Discovery of DNA dyes Hoechst 34580 and 33342 as good candidates for inhibiting amyloid beta formation: in silico and in vitro study

Nguyen Quoc Thai, Ning-Hsuan Tseng, Mui Thi Vu, Tin Trung Nguyen, Huynh Quang Linh, Chin-Kun Hu, Yun-Ru Chen, Mai Suan Li [QuangTrung Software City]

J.Comp.Aided. Mol.des. **30**, 639-650, 2016.

Combining Lipinski's rule with the docking and steered molecular dynamics simulations and using the PubChem data base of about 1.4 million compounds, we have obtained DNA dyes Hoechst 34580 and Hoechst 33342 as top-leads for the Alzheimer's disease. The binding properties of these ligands to amyloid beta ($A\beta$) fibril were thoroughly studied by in silico and in vitro experiments. Hoechst 34580 and Hoechst 33342 prefer to locate near hydrophobic regions with binding affinity mainly governed by the van der Waals interaction.

Mechanism for verification of mismatched and homoduplex DNAs by nucleotides-bound MutS analyzed by molecular dynamics simulations

Hisashi Ishida [Quantum Beam Science Research Directorate] and Atsushi Matsumoto

Proteins: Stru. Fun. & Bioinf., **84**, 1287–1303, 2016.

In order to understand how MutS recognizes mismatched DNA and induces the reaction of DNA repair using ATP, the dynamics of the complexes of MutS (bound to the ADP and ATP nucleotides, or not) and DNA (with mismatched and matched base-pairs) were investigated using molecular dynamics simulations. As for DNA, the structure of the base-pairs of the homoduplex DNA which interacted with the DNA recognition site of MutS was intermittently disturbed, indicating that the homoduplex DNA was unstable.

Protein – Nucleic Acid Interactions (Cont'd)

Improved Accuracy in RNA–Protein Rigid Body Docking by Incorporating Force Field for Molecular Dynamics Simulation into the Scoring Function

Junichi Iwakiri, Michiaki Hamada, Kiyoshi Asai, and Tomoshi Kameda [National Institute of Advanced Industrial Science and Technology (AIST)]

J. Chem. Theor. and Comp., **12**, 4688–4697, 2016.

RNA–protein interactions play fundamental roles in many biological processes. To understand these interactions, it is necessary to know the three-dimensional structures of RNA–protein complexes. However, determining the tertiary structure of these complexes is often difficult, suggesting that an accurate rigid body docking for RNA–protein complexes is needed. In this study, we focus on the former problem to improve the prediction accuracy in RNA–protein docking. Our method is based on the integration of physicochemical information about RNA into ZDOCK, which is known as one of the most successful computer programs for protein–protein docking.

Nucleic Acids

ProbFold: a probabilistic method for integration of probing data in RNA secondary structure prediction

Sudhakar Sahoo, Michał P. Świtnicki, and Jakob Skou Pedersen [Aarhus University Hospital]

Bioinformatics. **32**, 2626–2635, 2016.

Recently, new RNA secondary structure probing techniques have been developed, including Next Generation Sequencing based methods capable of probing transcriptome-wide. These techniques hold great promise for improving structure prediction accuracy. Here, we develop and explore a modular probabilistic approach for integrating probing data in RNA structure prediction. It can be automatically trained given a set of known structures with probing data. The approach is demonstrated on SHAPE datasets, where we evaluate and selectively model specific correlations. The approach often makes superior use of the probing data signal compared to other methods.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Structural and Physico-Chemical Interpretation (SPCI) of QSAR Models and Its Comparison with Matched Molecular Pair Analysis

Pavel Polishchuk [University Hospital in Olomouc], Oleg Tinkov, Tatiana Khristova, Ludmila Ognichenko, Anna Kosinskaya, Alexandre Varnek, and Victor Kuz'min

J. Chem. Infor. and Mod., **56**, 1455–1469, 2016.

This paper describes the Structural and Physico-Chemical Interpretation (SPCI) approach, which is an extension of a recently reported method for interpretation of quantitative structure–activity relationship (QSAR) models. This approach can efficiently be used to reveal structural motifs and the major physicochemical factors affecting the investigated properties. Its efficacy was demonstrated both on the classical Free–Wilson data set and on several data sets with different end points (permeability of the blood–brain barrier, fibrinogen receptor antagonists, acute oral toxicity).

Potentials and Parameters

Bottled SAFT: A Web App Providing SAFT- γ Mie Force Field Parameters for Thousands of Molecular Fluids

ÅsmundErvik, Andrés Mejía, and Erich A. Müller [Imperial College London]

J.Chem. Infor. and Mod., **56**,1609–1614, 2016.

Coarse-grained molecular simulation has become a popular tool for modeling simple and complex fluids alike. Because the number of molecular fluids of interest in nature and in engineering processes is immense, constructing force field parameter tables by individually fitting to experimental data is a futile task. A step to solve this challenge was taken by Mejía et al., who proposed a correlation that provides SAFT- γ Mie force field parameters for a fluid provided one knows the critical temperature, the acentric factor and a liquid density, all relatively accessible properties. Building on this, we applied the correlation to more than 6000 fluids, and constructed a web application, called “Bottled SAFT”.

Optimization of Protein Backbone Dihedral Angles by Means of Hamiltonian Reweighting

Christian Margreitter and Chris Oostenbrink [University of Natural Resources and Life Sciences]

J.Chem. Infor. and Mod., **56**,1823–1834, 2016.

Molecular dynamics simulations depend critically on the accuracy of the underlying force fields in properly representing biomolecules. Hence, it is crucial to validate the force-field parameter sets in this respect. In the context of the GROMOS force field, this is usually achieved by comparing simulation data to experimental observables for small molecules. In this study, we develop new amino acid backbone dihedral angle potential energy parameters based on the widely used 54A7 parameter set by matching to experimental J values and secondary structure propensity scales.

Predicting the Chemical Potential and Osmotic Pressure of Polysaccharide Solutions by Molecular Simulations

JörgSauter and Andrea Grafmüller [Max Planck Institute of Colloids and Interfaces]

J. Chem. Theor. and Comp, **12**, 4375–4384, 2016.

Differences in the chemical potential of water and the resulting osmotic pressure across semipermeable membranes are of fundamental importance for many biological systems. Here, we calculate the osmotic pressure and the chemical potential of water for polysaccharide solutions by molecular simulations. We set up a method to measure the osmotic pressure in polysaccharide systems at different concentrations and found that for monomers the experimental trend with respect to the solute concentration is reproduced correctly.

Simulating Replica Exchange: Markov State Models, Proposal Schemes, and the Infinite Swapping Limit

Bin W. Zhang, Wei Dai, Emilio Gallicchio, Peng He, Junchao Xia, Zhiqiang Tan, and Ronald M. Levy [Temple University, Philadelphia]

J. Phys. Chem. B., **120**, 8289–8301, 2016.

Replica exchange molecular dynamics is a multicanonical simulation technique commonly used to enhance the sampling of solvated biomolecules on rugged free energy landscapes. While replica exchange is relatively easy to implement, there are many unanswered questions about how to use this technique most efficiently, especially because it is frequently the case in practice that replica exchange simulations are not fully converged. We have constructed a Markov state model of replica exchange (MSMRE) using long molecular dynamics simulations of a host–guest binding system as an example, in order to study how different implementations of the replica exchange cycle can affect the sampling efficiency.

Molecular Dynamics

Exploring the Dynamics of the TWIK-1 Channel

Victoria Oakes, Simone Furini, David Pryde, Carmen Domene [University of Oxford, Oxford]

Biophysical Journal., **111**, 775-784, 2016.

Potassium channels in the two-pore domain family (K2P) have various structural attributes that differ from those of other K^+ channels, including a dimeric assembly constituted of nonidentical domains and an expansive extracellular cap. Crystallization of the prototypical K2P channel, TWIK-1, finally revealed the structure of these characteristics in atomic detail, allowing computational studies to be undertaken. In this study, we performed molecular-dynamics simulations for a cumulative time of $\sim 1 \mu s$ to discern the mechanism of ion transport throughout TWIK-1.

A mononuclear non-heme-iron dioxygen-carrying protein?

Amr A.A. Attia, Radu Silaghi-Dumitrescu [Babeş-Bolyai University, Cluj-Napoca]

J. Mol. Graph. and Mod., **69**, 103-110, 2016.

The ability of mononuclear non-heme iron complexes to function as molecular oxygen transporters is investigated by density functional theory. The factors governing the efficiency of the reversible binding of dioxygen at the active site of the dinuclear non-heme iron enzyme hemerythrin, including antiferromagnetic coupling and the conversion of dioxygen to hydroperoxo by a proton coupled 2-electron transfer mechanism, are revisited and considered as possible tools in mononuclear non-heme complexes.

Interaction studies of human prion protein (HuPrP109–111: methionine-lysine-histidine) tripeptide model with transition metal cations

C. Pitchumani Violet Mary, R. Shankar [Bharathiar University, Coimbatore], S. Vijayakumar, P. Kolandaivel

J. Mol. Graph. and Mod., **69**, 111-126, 2016.

In the present study, the coordination bonds between the Methionine-Lysine-Histidine (Ac-MKH-NHMe) tripeptide model associated with the fifth metal binding site, which triggers the β -sheet formation of human prion protein and the divalent metal cations such as Mn^{2+} , Cu^{2+} and Zn^{2+} were studied using B3LYP and M052X levels of theory with LANL2DZ basis set. For each transition divalent metal cation, three different coordination modes (4N, 3NO, and 2NSO) were analyzed. The present result reveals that overall structural parameters of MKH model tripeptide are altered due to the interaction of divalent metal cations.

Effect of External Electric Field on Substrate Transport of a Secondary Active Transporter

Ji-Long Zhang, Qing-Chuan Zheng, Li-Ying Yu, Zheng-Qiang Li, and Hong-Xing Zhang [Jilin University]

J. Chem. Infor. and Mod., **56**, 1539–1546, 2016.

Substrate transport across a membrane accomplished by a secondary active transporter (SAT) is essential to the normal physiological function of living cells. In the present research, a series of all-atom molecular dynamics (MD) simulations under different electric field (EF) strengths was performed to investigate the effect of an external EF on the substrate transport of an SAT. The results show that EF both affects the interaction between substrate and related protein's residues by changing their conformations and tunes the timeline of the transport event.

Molecular Dynamics (Cont'd)

Contribution of Electrostatics to the Kinetics of Electron Transfer from NADH-Cytochrome b5 Reductase to Fe(III)-Cytochrome b5

SireeshaKollipara, ShivakishoreTatireddy, ThusithaPathirathne, Lasantha K. Rathnayake, and Scott H. Northrup [Tennessee Technological University]

J. Phys. Chem. B., **120**, 8193–8207, 2016.

Brownian dynamics (BD) simulations provide here a theoretical atomic-level treatment of the reduction of human ferric cytochrome b5 (cyt b5) by NADH-cytochrome b5 reductase (cyt b5r) and several of its mutants. BD is used to calculate the second-order rate constant of electron transfer (ET) between the proteins for direct correlation with experiments. Interestingly, the inclusion of electrostatic forces dramatically increases the reaction rate of the native proteins despite the overall negative charge of both proteins.

Electrostatic Steering Accelerates C3d:CR2 Association

Rohith R. Mohan, Gary A. Huber, and Dimitrios Morikis [University of California, Riverside]

J. Phys. Chem. B., **120**, 8416–8423, 2016.

Electrostatic effects are ubiquitous in protein interactions and are found to be pervasive in the complement system as well. The interaction between complement fragment C3d and complement receptor 2 (CR2) has evolved to become a link between innate and adaptive immunity. Electrostatic interactions have been suggested to be the driving factor for the association of the C3d:CR2 complex. In this study, we investigate the effects of ionic strength and mutagenesis on the association of C3d:CR2 through Brownian dynamics simulations.

Action of Caffeine as an Amyloid Inhibitor in the Aggregation of A β 16–22 Peptides

Bhanita Sharma and Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **120**, 9019–9033, 2016.

Alzheimer's disease (AD) is a neurodegenerative disease caused due to aggregation of A β peptides in the brain tissues. Recently, several studies on AD transgenic mice have shown the effect of caffeine in significantly reducing the A β amyloid level in their brains. However, the mechanism and mode of caffeine action on amyloid aggregation are not known. Therefore, in this study, we have carried out molecular dynamics simulations of five amyloid-forming A β 16–22 peptides in pure water and in a regime of caffeine solutions, with different caffeine/peptide stoichiometric ratios.

Exploring the A22-Bacterial Actin MreB Interaction through Molecular Dynamics Simulations

Yaw Awuni, Shimin Jiang, Robert C. Robinson, and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B., **120**, 9867–9874, 2016.

MreB is an actin-like cytoskeleton protein that plays a vital role in the maintenance of the rod-shaped morphology of many bacteria. S-(3,4-Dichlorobenzyl) isothiourrea (A22) is an antibiotic-like small molecule that perturbs the rod cell shape and has been suggested to inhibit MreB by targeting ATP hydrolysis. However, without the elucidation of the structure of the ATP-bound state of MreB in the presence of A22, the mechanism of A22 inhibition is still not clear. Here we apply conventional molecular dynamics simulations to explore the dynamics of the active site of MreB in complex with A22 and different nucleotides.

Molecular Dynamics (Cont'd)

Fe²⁺ binding on amyloid β -peptide promotes aggregation

SubramaniamBoopathi and PonmalaiKolandaivel [Bharathiar University]

Proteins: Stru. Fun. & Bioinf., **84**, 1257–1274, 2016.

The metal ions Zn²⁺, Cu²⁺, and Fe²⁺ play a significant role in the aggregation mechanism of A β peptides. However, the nature of binding between metal and peptide has remained elusive; the detailed information on this from the experimental study is very difficult. Density functional theory (dft) (M06-2X/6-311++G (2df,2pd) +LANL2DZ) has employed to determine the force field resulting due to metal and histidine interaction. We performed 200 ns molecular dynamics (MD) simulation on A β 1-42-Zn²⁺, A β 1-42-Cu²⁺, and A β 1-42-Fe²⁺ systems in explicit water with different combination of coordinating residues including the three Histidine residues in the N-terminal.

Free Energy Perturbation

Application of Free Energy Perturbation for the Design of BACE1 Inhibitors

Myriam Ciordia, Laura Pérez-Benito, Francisca Delgado, Andrés A. Trabanco, and Gary Tresadern [Janssen Research and Development]

J.Chem. Infor. and Mod., **56**,1856–1871, 2016.

Novel spiroaminodihydropyrroles probing for optimized interactions at the P3 pocket of β -secretase 1 (BACE1) were designed with the use of free energy perturbation (FEP) calculations. The resulting molecules showed pIC₅₀ potencies in enzymatic BACE1 inhibition assays ranging from approximately 5 to 7. Good correlation was observed between the predicted activity from the FEP calculations and experimental activity. Simulations run with a default 5 ns approach delivered a mean unsigned error (MUE) between prediction and experiment of 0.58 and 0.91 kcal/mol for retrospective and prospective applications, respectively.

QM and QM/MM

Refined models of New Delhi metallo-beta-lactamase-1 with inhibitors: an QM/MM modeling study

Yeng-Tseng Wang [Kaohsiung Medical University] &Tian-Lu Cheng

J. Biomol. Stru. And Dyn., **34**,2214-2223, 2016.

New Delhi metallo-beta-lactamase 1 (NDM-1) has been identified as a potential target for the treatment of multi-drug resistance bacterial infections. We used molecular docking, normal MD, SIE, QM/MM MD simulations, QM/MM GBSA binding free energy, and QM/MM GBSA alanine-scanning mutagenesis techniques to investigate interactions of the NDM-1 with 11 inhibitors (Tigecycline, BAL30072, D-captopril, Penicillin G, Ampicillin, Carbenicillin, Cephalexin, Cefaclor, Nitrocefin, Meropenem, and Imipenem). From our normal MD and QM/MM simulations, the correlation coefficients between the predicted binding free energies and experimental values are .88 and .93, respectively.

QM and QM/MM (Cont'd)

Partial hessian fitting for determining force constant parameters in molecular mechanics

Ruixing Wang, Mikhail Ozhgibesov and Hajime Hirao
[Nanyang Technological University, Singapore]

J. Comp. Chem., **37**, 2349–2359, 2016.

We present a new protocol for deriving force constant parameters that are used in molecular mechanics (MM) force fields to describe the bond-stretching, angle-bending, and dihedral terms. A 3×3 partial matrix is chosen from the MM Hessian matrix in Cartesian coordinates according to a simple rule and made as close as possible to the corresponding partial Hessian matrix computed using quantum mechanics (QM). This partial Hessian fitting (PHF) is done analytically and thus rapidly in a least-squares sense, yielding force constant parameters as the output.

High-Efficiency Microiterative Optimization in QM/MM Simulations of Large Flexible Systems

Yan Zhang, Peng Xie, Xiaohu He, and Keli Han [Dalian Institute of Chemical Physics]

J. Chem. Theor. and Comp, **12**, 4632–4643, 2016.

We present here a double-optimizations-of-buffer-region (DOBR) microiterative scheme for high-efficiency energy minimizations of large, flexible systems in combined quantum-mechanical/molecular-mechanical (QM/MM) calculations. In the DOBR scheme, an entire system is divided into three regions: the core, buffer, and outer regions. The core region includes QM atoms and the MM atoms within a cutoff distance R_1 to the QM atoms (denoted by MM_1 atoms), and the buffer region consists of MM atoms within another cutoff distance R_2 to MM_1 atoms.

Laccase Redox Potentials: pH Dependence and Mutants, a QM/MM Study

Jan P. Götz and Michael Bühl [University of St Andrews, North Haugh]

J. Phys. Chem. B., **120**, 9265–9276, 2016.

We have studied the *T. versicolor* laccase T1 site redox potential (RP) at the M06/6-311++G**/SDD(Cu) level of theory, employing QM/MM-optimized geometries (RI-BP86/def2-SVP/def2-TZVP(Cu):CHARMM) of the whole protein system with electronic embedding. The oxidation state of the trinuclear cluster was found to affect the T1 site RP by about 0.2–0.3 V, depending on the protein protonation state. The computed laccase RP can be drastically lowered upon introduction of a protonation state corresponding to a neutral environment, by up to –1.37 V, which is likely an overestimation of the effect in vivo.

Characterizing the Structures, Spectra, and Energy Landscapes Involved in the Excited-State Proton Transfer Process of Red Fluorescent Protein LSSmKate1

Fasheng Chen, Qiao Zeng, Wei Zhuang, and WanZhen Liang
[Xiamen University]

J. Phys. Chem. B., **120**, 9833–9842, 2016.

By applying molecular dynamics (MD) simulations and quantum chemical calculations, we have characterized the states and processes involved in the excited-state proton transfer (ESPT) of LSSmKate1. MD simulations identify two stable structures in the electronic ground state of LSSmKate1, one with a protonated chromophore and the other with a deprotonated chromophore, thus leading to two separate low-energy absorption maxima with a large energy spacing, as observed in the calculated and experimentally measured absorption spectra.

QM and QM/MM (Cont'd)

Exploring the Dependence of QM/MM Calculations of Enzyme Catalysis on the Size of the QM Region

Garima Jindal and Arieh Warshel [University of Southern California]

J. Phys. Chem. B., **120**, 9913–9921, 2016.

Although QM/MM calculations are the primary current tool for modeling enzymatic reactions, the reliability of such calculations can be limited by the size of the QM region. Thus, we examine in this work the dependence of QM/MM calculations on the size of the QM region, using the reaction of catechol-O-methyl transferase (COMT) as a test case. Our study focuses on the effect of adding residues to the QM region on the activation free energy, obtained with extensive QM/MM sampling.

Comparative or Homology Modeling

Benchmarking the next generation of homology inference tools

Ganapathi Varma Saripella, Erik L. L. Sonnhammer, and Kristoffer Forslund [European Molecular Biology Laboratory]

Bioinformatics. **32**, 2636–2641, 2016.

Over the last decades, vast numbers of sequences were deposited in public databases. Bioinformatics tools allow homology and consequently functional inference for these sequences. New profile-based homology search tools have been introduced, allowing reliable detection of remote homologs, but have not been systematically benchmarked. We generated challenging benchmark datasets based on protein domain architectures within either the PFAM + Clan, SCOP/Superfamily or CATH/Gene3D domain definition schemes.

Bayesian nonparametrics in protein remote homology search

Mindaugas Margelevičius [Vilnius University]

Bioinformatics. **32**, 2744–2752, 2016.

Wide application of modeling of three-dimensional protein structures in biomedical research motivates developing protein sequence alignment computer tools featuring high alignment accuracy and sensitivity to remotely homologous proteins. In this paper, we aim at improving the quality of alignments between sequence profiles, encoded multiple sequence alignments. We develop a hierarchical Dirichlet process mixture model to describe the distribution of profile contexts, which is able to capture dependencies between amino acids in each context position.

Ligand Docking

Fragment-Based Analysis of Ligand Dockings Improves Classification of Actives

Richard K. Belew [University of California San Diego, La Jolla], Stefano Forli, David S. Goodsell, T. J. O'Donnell, and Arthur J. Olson

J. Chem. Inform. and Mod., **56**, 1597–1607, 2016.

We describe ADChemCast, a method for using results from virtual screening to create a richer representation of a target binding site, which may be used to improve ranking of compounds and characterize the determinants of ligand–receptor specificity. ADChemCast clusters docked conformations of ligands based on shared pairwise receptor–ligand interactions within chemically similar structural fragments, building a set of attributes characteristic of binders and nonbinders.

Ligand Docking (Cont'd)

Prediction of Protein Pairs Sharing Common Active Ligands Using Protein Sequence, Structure, and Ligand Similarity

Yu-Chen Chen, Robert Tolbert, Alex M. Aronov, Georgia McGaughey, W. Patrick Walters, and LidioMeireles [Vertex Pharmaceuticals Incorporated]

J.Chem. Infor. and Mod., **56**,1734–1745, 2016.

We benchmarked the ability of comparative computational approaches to correctly discriminate protein pairs sharing a common active ligand (positive protein pairs) from protein pairs with no common active ligands (negative protein pairs). Since the target and the off-targets of a drug share at least a common ligand, i.e., the drug itself, the prediction of positive protein pairs may help identify off-targets. We evaluated representative protein-centric and ligand-centric approaches, including (1) 2D and 3D ligand similarity, (2) several measures of protein sequence similarity in conjunction with different sequence sources (e.g., full protein sequence versus binding site residues), and (3) a newly described pocket shape similarity and alignment program called SiteHopper.

Molecular Mechanism of Biased Ligand Conformational Changes in CC Chemokine Receptor 7

ZiedGaieb, David D. Lo, and Dimitrios Morikis [University of California, Riverside]

J.Chem. Infor. and Mod., **56**,1808–1822, 2016.

Biased ligand binding to G protein-coupled receptors enables functional selectivity of intracellular effectors to mediate cellular function. Despite the significant advances made in characterizing the conformational states (transmembrane helical arrangements) capable of discriminating between G protein and arrestin binding, the role of the ligand in stabilizing such conformations remains unclear. To address this issue, we simulate microsecond dynamics of CC chemokine receptor 7 (CCR7) bound to its native biased ligands, CCL19 and CCL21, and detect a series of molecular switches that are mediated by various ligand-induced allosteric events.

mRAISE: an alternative algorithmic approach to ligand-based virtual screening

Mathias M. von Behren, Stefan Bietz, Eva Nittinger, Matthias Rarey[University of Hamburg]

J.Comp.Aided. Mol.des. **30**, 583-594, 2016.

Ligand-based virtual screening is a well established method to find new lead molecules in today's drug discovery process. In order to be applicable in day to day practice, such methods have to face multiple challenges. Many algorithms for ligand-based virtual screening have been proposed in the past, most of them based on pairwise comparisons. Here, a new method is introduced called mRAISE. Based on structural alignments, it uses a descriptor-based bitmap search engine (RAISE) to achieve efficiency.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 69, September, 2016.

- 1-7 **Development and targeting of transcriptional regulatory network controlling FLU1 activation in *Candida albicans* for novel antifungals**, AnubhutiJha, Awanish Kumar [National Institute of Technology Raipur]

See Applications / Medicinal Chemmistry and Drug Design.

- 8-16 **A comparative theoretical study of CO oxidation reaction by O₂ molecule over Al- or Si-decorated graphene oxide**, Mehdi D. Esrafil [University of Maragheh, Maragheh], FahimehSharifi, ParisaNematollahi

Using density functional theory calculations, the probable CO oxidation reaction mechanisms are investigated over Al- or Si-decorated graphene oxide (GO). The equilibrium geometry and electronic structure of these metal decorated-GOs along with the O₂/CO adsorption configurations are studied in detail.

- 17-25 **Molecular basis of the recognition of FMN by a HAD phosphatase TON_0338**, Rui-Juan Niu, Qing-Chuan Zheng [Jilin University, Changchun], Hong-Xing Zhang

See Applications / Enzyme Catalysis.

- 26-38 **Adsorption of poly(ethylene succinate) chain onto graphene nanosheets: A molecular simulation**, PayamKelich, Ahmad Asadinezhad [Isfahan University of Technology]

Understanding the interaction between single polymer chain and graphene nanosheets at local and global length scales is essential for it underlies the mesoscopic properties of polymer nanocomposites. A computational attempt was then performed using atomistic molecular dynamics simulation to gain physical insights into behavior of a model aliphatic polyester, poly(ethylene succinate), single chain near graphene nanosheets, where the effects of the polymer chain length, graphene functionalization, and temperature on conformational properties of the polymer were studied comparatively.

- 39-60 **The molecular shape and the field similarities as criteria to interpret SAR studies for fragment-based design of platinum(IV) anticancer agents. Correlation of physicochemical properties with cytotoxicity**, Julia Lorenzo, Ángel M. Montaña [Universidad de Barcelona]

Molecular shape similarity and field similarity have been used to interpret, in a qualitative way, the structure-activity relationships in a selected series of platinum(IV) complexes with anticancer activity. MM and QM calculations have been used to estimate the electron density, electrostatic potential maps, partial charges, dipolar moments and other parameters to correlate the stereo-electronic properties with the differential biological activity of complexes.

- 61-71 **Molecular dynamics simulation study: The decryption of bi and tri aromatics behavior with NaX zeolite**, M. HaghighiAsl [Ferdowsi University of Mashhad], F. Moosavi, J. Sargolzaei, Kh. Sharifi

See Applications / Zeolites.

- 72-77 **Simulations reveal increased fluctuations in estrogen receptor-alpha conformation upon antagonist binding**, Ho Leung Ng [University of Hawaii Cancer Center]

See Applications / Ligand Binding.

- 78-91 **In-silico screening for anti-Zika virus phytochemicals**, Kendall G. Byler, Ifedayo Victor Ogungbe, William N. Setzer [University of Alabama in Huntsville]

Zika virus (ZIKV) is an arbovirus that has infected hundreds of thousands of people and is a rapidly expanding epidemic across Central and South America. ZIKV infection has caused serious, albeit rare, complications including Guillain-Barré syndrome and congenital microcephaly. In this work, we have carried out an *in-silico* search for potential anti-Zika viral agents from natural sources.

- 92-102 **Mutagenicity of heteroaromatic amines: Computational study on the influence of methyl substituents**, Gabriela L. Borosky [Ciudad Universitaria, Córdoba]

Quantum mechanical calculations were performed to elucidate the factors determining the variations in mutagenic activity within groups of isomeric heteroaromatic amines that differ in the position of methyl substituents. Formation energies for noncovalent complexes and covalent DNA adducts were evaluated by means of high level quantum chemical methods.

- 103-110 **A mononuclear non-heme-iron dioxygen-carrying protein?**, Amr A.A. Attia, Radu Silaghi-Dumitrescu [Babeş-Bolyai University, Cluj-Napoca]

See Methodology / Molecular Dynamics.

- 111-126 **Interaction studies of human prion protein (HuPrP109–111: methionine-lysine-histidine) tripeptide model with transition metal cations**, C. Pitchumani Violet Mary, R. Shankar [Bharathiar University, Coimbatore], S. Vijayakumar, P. Koldaivel

See Methodology / Molecular Dynamics.

- 144-153 **Hydration of ligands of influenza virus neuraminidase studied by the fragment molecular orbital method**, Kana Tokuda, Chiduru Watanabe, Yoshio Okiyama, Yuji Mochizuki, Kaori Fukuzawa [The University of Tokyo], Yuto Komeiji

The fragment molecular orbital (FMO) method was applied to quantum chemical calculations of neuraminic acid, the natural substrate of the influenza virus neuraminidase, and two of its competitive inhibitors, Oseltamivir (Tamiflu®) and Zanamivir (Relenza®), to investigate their hydrated structures and energetics.

Journal of Computational Chemistry, 37 (25), September, 2016.

- 2249–2259 **Geometrical control of the interatomic coulombic decay process in quantum dots for infrared photodetectors**, PraphasiriDolbundalchok, Daniel Peláez, Emad F. Aziz and Annika Bande [Universität Heidelberg]

In electron dynamics calculations the interatomic Coulombic decay (ICD) process has recently been shown to take place in two vertically-aligned quantum dots (QDs). Energy emitted during the relaxation of one electron in one QD is converted into kinetic energy of another electron ejected from a neighboring QD. As the electronic structure of QDs can be controlled by their geometries, we prove here in thorough scans of the transversal and vertical QD confinement potentials' widths that geometries are likewise control parameters for ICD.

- 2260–2265 **Local electric dipole moments: A generalized approach**, Lynn Groß and Carmen Herrmann [University of Hamburg, Hamburg]

We present an approach for calculating local electric dipole moments for fragments of molecular or supramolecular systems. This is important for understanding chemical gating and solvent effects in nanoelectronics, atomic force microscopy, and intensities in infrared spectroscopy.

- 2266–2278 **Stability of functionalized corannulene cations [R-C₂₀H₁₀]⁺: An influence of the nature of R-Group**, Jingbai Li, Giovana da Silva Ramos and Andrey Yu Rogachev [Illinois Institute of Technology, Chicago]

The first comprehensive theoretical study of stability of *hub*-functionalized corannulene cations [R-C₂₀H₁₀]⁺ as the function of the nature of R-group was accomplished. The initial set of linear alkyl R-group of different length (R=(CH₂)_nCH₃, *n* = 0–9) was augmented by groups which form stable organic cations, such as *tert*-butyl, isopropyl, allyl, and phenyl.

- 2279–2303 **A generalized operational formula based on total electronic densities to obtain 3D pictures of the dual descriptor to reveal nucleophilic and electrophilic sites accurately on closed-shell molecules**, Jorge I. Martínez-Araya [Universidad Andres Bello]

By means of the conceptual density functional theory, the so-called dual descriptor (DD) has been adapted to be used in any closed-shell molecule that presents degeneracy in its frontier molecular orbitals.

- 2304–2315 **Informatics-Based Energy Fitting Scheme for Correlation Energy at Complete Basis Set Limit**, Junji Seino and Hiromi Nakai [Waseda University, Shinjuku-Ku]

Energy fitting schemes based on informatics techniques using hierarchical basis sets with small cardinal numbers were numerically investigated to estimate correlation energies at the complete basis set limits.

- 2316–2323 **The nature of structure and bonding between transition metal and mixed Si-Ge tetramers: A 20-electron superatom system**, Xiaojun Li [Xi'an University, Xi'an], Zhijun Yan and Shuna Li

A novel superatom species with 20-electron system, Si_xGe_yM⁺ (*x* + *y* = 4; M = Nb, Ta), was properly proposed. The trigonal bipyramid structures for the studied systems were identified as the putative global minimum by means of the density functional theory calculations.

Journal of Computational Chemistry, 37 (26), October, 2016.

- 2341–2348 **Water molecules inside protein structure affect binding of monosaccharides with HIV-1 antibody 2G12**, Kaori Ueno-Noto [Kitasato University, Minami-Ku] and Keiko Takano

See Applications / Water and Solvation

- 2349–2359 **Partial hessian fitting for determining force constant parameters in molecular mechanics**, Ruixing Wang, Mikhail Ozhgibesov and Hajime Hirao [Nanyang Technological University, Singapore]

See Methodology / QM and QM/MM.

- 2360–2373 **Predicting Pt-195 NMR chemical shift using new relativistic all-electron basis set**, D. Paschoal, C. Fonseca Guerra, M. A. L. de Oliveira, T. C. Ramalho and H. F. Dos Santos [Universidade Federal de Juiz de Fora]

Predicting NMR properties is a valuable tool to assist the experimentalists in the characterization of molecular structure. For heavy metals, such as Pt-195, only a few computational protocols are available. In the present contribution, all-electron Gaussian basis sets, suitable to calculate the Pt-195 NMR chemical shift, are presented for Pt and all elements commonly found as Pt-ligands.

- 2374–2385 **Accurate adsorption energies for small molecules on oxide surfaces: CH₄/MgO(001) and C₂H₆/MgO(001)**, A. Daniel Boese and Joachim Sauer [Humboldt-Universität zu Berlin, Berlin]

A hybrid method is applied that combines second order Møller–Plesset perturbation theory (MP2) for cluster models with density functional theory for periodic (slab) models to obtain structures and energies for methane and ethane molecules adsorbed on the MgO(001) surface.

- 2386–2394 **Mechanistic insight on (E)-methyl 3-(2-aminophenyl)acrylate cyclization reaction by multicatalysis of solvent and substrate**, Jiahui Liu, Yiyang Zheng, Ying Liu, Haiyan Yuan and Jingping Zhang [Northeast Normal University, Changchun]

The reaction mechanism of (E)-methyl 3-(2-aminophenyl)acrylate (**A**) with phenylisothiocyanate (**B**) as well as the vital roles of substrate **A** and solvent water were investigated under unassisted, water-assisted, substrate **A**-assisted, and water-**A**-assisted conditions.

- 2395–2402 **Ab initio potential energy surface and vibration-rotation energy levels of silicon dicarbide, SiC₂**, Jacek Koput [Adam Mickiewicz University, Poznań]

The accurate ground-state potential energy surface of silicon dicarbide, SiC₂, has been determined from *ab initio* calculations using the coupled-cluster approach. Results obtained with the conventional and explicitly correlated coupled-cluster methods were compared.

Journal of Computational Chemistry, 37 (27), October, 2016.

- 2409–2422 **Incorporation of local structure into kriging models for the prediction of atomistic properties in the water decamer**, Stuart J Davie, Nicodemo Di Pasquale and Paul L. A. Popelier [University of Manchester, Oxford Road]

Machine learning algorithms have been demonstrated to predict atomistic properties approaching the accuracy of quantum chemical calculations at significantly less computational cost. Difficulties arise, however, when attempting to apply these techniques to large systems, or systems possessing excessive conformational freedom. In this article, the machine learning method kriging is applied to predict both the intra-atomic and interatomic energies, as well as the electrostatic multipole moments, of the atoms of a water molecule at the center of a 10 water molecule (decamer) cluster.

- 2423–2435 **Adding energy minimization strategy to peptide-design algorithm enables better search for RNA-binding peptides: Redesigned λ N peptide binds boxB RNA**, Xingqing Xiao, Michelle E. Hung, Joshua N. Leonard and Carol K. Hall [North Carolina State University, Raleigh]

See Applications / Protein-Nucleic acids.

- 2436–2446 **Calculating protein–ligand binding affinities with MMPBSA: Method and error analysis**, Changhao Wang, Peter H. Nguyen, Kevin Pham, Danielle Huynh, Thanh-Binh Nancy Le, Hongli Wang, Pengyu Ren and Ray Luo [Chemical and Materials Physics Graduate Program, Irvine]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

- 2447–2453 **Explicitly correlated frequency-independent second-order green's function for accurate ionization energies**, Yu-ya Ohnishi and Seichiro Ten-no [Kobe University, Nada-Ku]

Explicitly correlated second-order Green's function (GF2-F12) is presented and applied to polycyclic aromatic hydrocarbons (PAHs), oligothiophene, and porphyrins. GF2 suffers from slow convergence of orbital expansions as in the ordinary post Hartree–Fock methods in *ab initio* theory, albeit the method is capable of providing quantitatively accurate ionization energies (IE) near the complete basis set limit.

- 2454–2466 **Description of excited states in [Re(Imidazole)(CO)₃(Phen)]⁺ including solvent and spin-orbit coupling effects: Density functional theory versus multiconfigurational wavefunction approach**, Maria Fumanal and Chantal Daniel [Institut De Chimie Strasbourg]

The low-lying electronic excited states of [Re(imidazole)(CO)₃(phen)]⁺ (phen = 1,10-phenanthroline) ranging between 420 nm and 330 nm have been calculated by means of relativistic spin-orbit time-dependent density functional theory (TD-DFT) and wavefunction approaches (state-average-CASSCF/CASPT2).

- 2467–2478 **Reaction rates in a theory of mechanochemical pathways**, Wolfgang Quapp [University Leipzig, Leipzig] and Josep Maria Bofill

If one applies mechanical stress to a molecule in a defined direction then one generates a new, effective potential energy surface (PES). Changes for minima and saddle points (SP) by the stress are described by Newton trajectories on the original PES (Quapp and Bofill, Theor. Chem. Acc. 2016, 135, 113). The barrier of a reaction fully breaks down for the maximal value of the norm of the gradient of the PES along a pulling

Newton trajectory. We discuss simple, two-dimensional examples for this model to understand more deeply the mechanochemistry of molecular systems under a mechanical stress.

Journal of Computational Chemistry, 37 (28), October, 2016.

- 2485–2494 **Exponential repulsion improves structural predictability of molecular docking**, Václav Bazgier, Karel Berka, Michal Otyepka and Pavel Banáš [Palacký University Olomouc]

Molecular docking is a powerful tool for theoretical prediction of the preferred conformation and orientation of small molecules within protein active sites. Here, we present implementation and testing of a scoring function based on more physically justified exponential repulsion instead of the standard Lennard–Jones potential.

- 2495–2507 **Electrostatic component of binding energy: Interpreting predictions from poisson–boltzmann equation and modeling protocols**, Arghya Chakravorty, Lin Li and Emil Alexov [Clemson University, Clemson]

Macromolecular interactions are essential for understanding numerous biological processes and are typically characterized by the binding free energy. Important component of the binding free energy is the electrostatics, which is frequently modeled via the solutions of the Poisson–Boltzmann Equations (PBE). We argue that the sensitivity of the absolute $\Delta\Delta G_{\text{elec}}$ calculated with PBE using different input parameters and definitions does not indicate PBE deficiency, rather this is what should be expected.

- 2508–2517 **A stress tensor and QTAIM perspective on the substituent effects of biphenyl subjected to torsion**, D. Jiajun, J. R. Maza, Y. Xu, T. Xu, R. Momen, S. R. Kirk and S. Jenkins [Hunan Normal University, Changsha Hunan]

The Quantum Theory of Atoms in Molecules (QTAIM) defines quantities in 3D space that can be easily obtained from routine quantum chemical calculations. The present investigation shows that local properties can be related quantitatively to measures traditionally connected to experimental data, such as Hammett constants.

- 2518–2526 **Density functional theory for molecular and periodic systems using density fitting and continuous fast multipole method: Analytical gradients**, Roman Łazarski, Asbjörn Manfred Burow, Lukáš Grajciar and Marek Sierka [Friedrich-Schiller-Universität Jena]

A full implementation of analytical energy gradients for molecular and periodic systems is reported in the TURBOMOLE program package within the framework of Kohn–Sham density functional theory using Gaussian-type orbitals as basis functions.

- 2527–2536 **Structure and properties of iron oxide clusters: From Fe_6 to Fe_6O_{20} and from Fe_7 to Fe_7O_{24}** , Gennady L. Gutsev [Florida A&M University, Tallahassee], Kalayu G. Belay, Lavrenty G. Gutsev and Bala R. Ramachandran

Geometrical and electronic structures of the neutral and singly negatively charged Fe_6O_n and Fe_7O_m clusters in the range of $1 \leq n \leq 20$ and $1 \leq m \leq 24$, respectively, are computed using density functional theory with the generalized gradient approximation. The largest clusters in the two series, Fe_6O_{20} and Fe_7O_{24} , can be described as $\text{Fe}(\text{FeO}_4)_5$ and $\text{Fe}(\text{FeO}_4)_6$ or alternatively as $[\text{FeO}_5](\text{FeO}_3)_5$ and $[\text{FeO}_6](\text{FeO}_3)_6$, respectively.

- 2537–2546 **Horizontal vectorization of electron repulsion integrals**, Benjamin P. Pritchard and Edmond Chow [Georgia Institute of Technology, Atlanta]

We present an efficient implementation of the Obara–Saika algorithm for the computation of electron repulsion integrals that utilizes vector intrinsics to calculate several primitive integrals concurrently in a SIMD vector. Initial benchmarks display a 2–4 times speedup with AVX instructions over comparable scalar code, depending on the basis set.

Journal of Molecular Modeling, 22 (10), October, 2016.

- 233 **Different transport behaviors of NH_4^+ and NH_3 in transmembrane cyclic peptide nanotubes**, Mingming Zhang, Jianfen Fan [Soochow University], Jian Xu, Peipei Weng, Huifang Lin

Two water-filled transmembrane cyclic peptide nanotubes (CPNTs) of $8 \times \text{cyclo}-(\text{WL})_{n=4,5}/\text{POPE}$ were chosen to investigate the dependences of the transport properties of the positive NH_4^+ and neutral NH_3 on the channel radius. Molecular dynamic simulations revealed that molecular charge, size, ability to form H-bonds and channel radius all significantly influence the behaviors of NH_4^+ and NH_3 in a CPNT.

- 234 **Parameterization and optimization of the menthol force field for molecular dynamics simulations**, Mateusz Jasik, Borys Szeftczyk [Wrocław University of Technology]

Menthol's various biological properties render it a useful component for medical and cosmetological applications, while its three centers of asymmetry mean that it can be used in a range of organic reactions. Menthol-substituted ionic liquids (ILs) have been found to exhibit promising antimicrobial and antielectrostatic properties, as well as being useful in organic catalysis and biochemical studies.

- 235 **Mechanistic investigation of the uncatalyzed esterification reaction of acetic acid and acid halides with methanol: a DFT study**, Monsurat M. Lawal, Thavendran Govender, Glenn E. M. Maguire, Bahareh Honarparvar, Hendrik G. Kruger [University of KwaZulu-Natal]

Implementation of catalysts to drive reactions from reactants to products remains a burden to synthetic and organic chemists. In spite of investigations into the kinetics and mechanism of catalyzed esterification reactions, less effort has been made to explore the possibility of an uncatalyzed esterification process.

- 236 **Exploring ligand dissociation pathways from aminopeptidase N using random acceleration molecular dynamics simulation**, Ya Liu, GuoGang Tu [NanChang University], XiaoPing Lai, BinHai Kuang, ShaoHua Li

See Applications / Enzyme Catalysis.

- 237 **Theoretical study on the metabolic mechanisms of levomepromazine by cytochrome P450**, Yongting Wang, Qiu Chen, Zhiyu Xue, Yan Zhang, Zeqin Chen [China West Normal University Nanchong], Zhiyu Xue, Yan Zhang, Zeqin Chen, Ying Xue

See Applications / Medicinal Chemistry and Drug Design.

- 238 **Putative membrane lytic sites of P-type and S-type cardiotoxins from snake venoms as probed by all-atom molecular dynamics simulations**, Biswajit Gorai, Muthusamy Karthikeyan, Thirunavukkarasu Sivaraman [SASTRA University Thanjavur]

See Applications / Medicinal Chemistry and Drug Design.

- 239 **MOLS 2.0: software package for peptide modeling and protein–ligand docking**, D. Sam Paul, N. Gautham [University of Madras, Chennai]

See Applications / Bioinformatics.

- 240 **Theoretical investigation of loratadine reactivity in order to understand its degradation properties: DFT and MD study**, Stevan Armaković [University of Novi Sad], Sanja J. Armaković, Biljana F. Abramović

See Applications / Medicinal Chemistry and Drug Design.

- 241 **Theoretical investigation on exciton-dissociation and charge-recombination processes of PC₆₁BM-PTDPPSe interface**, Caibin Zhao, Hongguang Ge, Lingxia Jin, Qiang Zhang [Shaanxi University of Technology, Hanzhong], Zhanling Wang, Wenliang Wang, Shiwei Yin

Designing and synthesizing novel electron-donor polymers with the high photovoltaic performances has remained a major challenge and hot issue in organic electronics. In this work, the exciton-dissociation (k_{dis}) and charge-recombination (k_{rec}) rates for the PC₆₁BM-PTDPPSe system as a promising polymer-based solar cell candidate have been theoretically investigated by means of density functional theory (DFT) calculations coupled with the non-adiabatic Marcus charge transfer model.

- 242 **PyCPR – a python-based implementation of the Conjugate Peak Refinement (CPR) algorithm for finding transition state structures**, Florian J. Gisdon, Martin Culka, G. Matthias Ullmann [University of Bayreuth]

Conjugate peak refinement (CPR) is a powerful and robust method to search transition states on a molecular potential energy surface. Nevertheless, the method was to the best of our knowledge so far only implemented in CHARMM. In this paper, we present PyCPR, a new Python-based implementation of the CPR algorithm within the pDynamo framework. We provide a detailed description of the theory underlying our implementation and discuss the different parts of the implementation. The method is applied to two different problems.

- 244 **In silico structural characterization of protein targets for drug development against Trypanosoma cruzi**, Carlyle Ribeiro Lima, Nicolas Carels, Ana Carolina Ramos Guimaraes, Pierre Tufféry, Philippe Derreumaux [Instituto Oswaldo Cruz (IOC), FIOCRUZ]

See Applications / Medicinal Chemistry and Drug Design.

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- 245 **Theoretical study of penta- and heteropentadienyl beryllium complexes coordinated to hydrogen molecules**, Sharity Morales-Meza, Nancy Pérez-Peralta, M. Esther Sanchez-Castro, Mario Sanchez [Centro de Investigación en Materiales Avanzados, Apodaca]

A series of penta- and heteropentadienyl $[\text{CH}_2\text{CHCHCHXBe}]^+$, ($\text{X} = \text{CH}_2, \text{O}, \text{NH}, \text{S}$) complexes has been theoretically studied. All calculated complexes show beryllium atoms with two, three, and five coordination numbers.

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About 95 Papers from more than 30 Journals are cited.

1	APPLICATIONS (66)	Page 2		
1.1	Small Molecules (9)			
	Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 4
1.2	Biopolymers (57)			
	Bioinformatics and Cheminformatics	Page 5	Enzyme Catalysis	Page 14
	Comparative or Homology Modeling	Page 6	Protein-Protein Interactions	Page 16
	Protein Conformational Analysis	Page 6	Membrane Proteins	Page 17
	Protein Structure Analysis	Page 8	Protein Folding	Page 18
	Protein Dynamics	Page 8	Protein-Nucleic Acids	Page 18
	Ligand Binding	Page 10	Nucleic Acids	Page 19
1.3	Polymers			
1.4	Surfaces, Catalysts and Material			
2	METHODOLOGY (13)	Page 20		
	QSAR	Page 20	Comparative or Homology	Page 21
	Molecular Dynamics	Page 20	Ligand Docking	Page 22
	QM & QM/MM	Page 21		
3	JOURNAL REVIEWS (5)	Page 24		
	Journal of Molecular Graphics and Modeling, 70, November, 2016.			
	Journal of Computational Chemistry, 37 (29, 30), November, 2016.			
	Journal of Molecular Modeling, 22 (11), November, 2016.			
	Molecular Simulation, 42 (17), September, 2016.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 32		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Computer-aided discovery of anti-HIV agents

William L. Jorgensen [Yale University, New Haven]

Bioorg. and Med. Chem., **24**, 4768-4778, 2016

A review is provided on efforts in our laboratory over the last decade to discover anti-HIV agents. The work has focused on computer-aided design and synthesis of non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs) with collaborative efforts on biological assaying and protein crystallography. Numerous design issues were successfully addressed including the need for potency against a wide range of viral variants, good aqueous solubility, and avoidance of electrophilic substructures.

A molecular dynamics simulation investigation of the relative stability of the cyclic peptide octreotide and its deprotonated and its (CF₃)-Trp substituted analogs in different solvents

Lorna J. Smith, Georgia Rought Whitta, Jožica Dolenc, Dongqi Wang, Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

Bioorg. and Med. Chem., **24**, 4936-4948, 2016

The cyclic octa-peptide octreotide and its derivatives are used as diagnostics and therapeutics in relation to particular types of cancers. This led to investigations of their conformational properties using spectroscopic, NMR and CD, methods. A CF₃-substituted derivative, that was designed to stabilize the dominant octreotide conformer responsible for receptor binding, turned out to have a lower affinity. In this article, we use MD simulation without and with time-averaged NOE distance and time-averaged local-elevation 3J-coupling restraining representing experimental NMR data to determine the conformational properties of the different peptides in the different solvents for which experimental data are available.



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Medicinal Chemistry and Drug Design (Cont'd)

Molecular docking and structure-based virtual screening studies of potential drug target, CAAX prenyl proteases, of Leishmania donovani

Shalini Singh, Sitirarasu Vijaya Prabhu, Venkatesan Suryanarayanan, Ruchika Bhardwaj, Sanjeev Kumar Singh & Vikash Kumar Dubey [Indian Institute of Technology Guwahati]

J. Biomol. Stru. And Dyn., **34**, 2367-2386, 2016.

Targeting CAAX prenyl proteases of Leishmania donovani can be a good approach towards developing a drug molecule against Leishmaniasis. We have modeled the structure of CAAX prenyl protease I and II of L. donovani, using homology modeling approach. The structures were further validated using Ramachandran plot and ProSA. Active site prediction has shown difference in the amino acid residues present at the active site of CAAX prenyl protease I and CAAX prenyl protease II.

A comparative modeling and molecular docking study on Mycobacterium tuberculosis targets involved in peptidoglycan biosynthesis

Zeynab Fakhar, Suhashni Naiker, Claudio N. Alves, Thavendran Govender, Glenn E.M. Maguire, Jeronimo Lameira, Gyanu Lamichhane, Hendrik G. Kruger & Bahareh Honarparvar [University of KwaZulu-Natal]

J. Biomol. Stru. And Dyn., **34**, 2399-2417, 2016.

An alarming rise of multidrug-resistant Mycobacterium tuberculosis strains and the continuous high global morbidity of tuberculosis have reinvigorated the need to identify novel targets to combat the disease. The enzymes that catalyze the biosynthesis of peptidoglycan in M. tuberculosis are essential and noteworthy therapeutic targets. In this study, the biochemical function and homology modeling of MurI, MurG, MraY, DapE, DapA, Alr, and Ddl enzymes of the CDC1551 M. tuberculosis strain involved in the biosynthesis of peptidoglycan cell wall are reported.

Identification of non-resistant ROS-1 inhibitors using structure based pharmacophore analysis

Disha Pathak, Navriti Chadha, Om Silakari [Punjabi University, Patiala]

J. Mol.Graph. and Mod., **69**, 85-93, 2016.

Proto-oncogene receptor tyrosine kinase ROS-1 plays a key role in regulating a variety of cancers mainly non-small cell lung cancer (NSCLC). The marketed ROS-1 inhibitors such as Crizotinib suffer from the tribulations of growing resistance due to mutations primarily Gly2032Arg in the ROS-1 protein. The present study was designed to identify inhibitors against wild type (WT) as well as mutant ROS-1 protein that will offer a broader spectrum of activity.

In silico approaches and proportional odds model towards identifying selective ADAM17 inhibitors from anti-inflammatory natural molecules

Pallab Kumar Borah, Sourav Chakraborty, Anupam N. Jha, Sanchaita Rajkhowa, Raj Kumar Duary [Tezpur University, Napaam]

J. Mol.Graph. and Mod., **69**, 129-139, 2016.

ADAM metalloproteinase domain 17 (ADAM17) is an attractive target for the development of new anti-inflammatory drugs. We aimed to identify selective inhibitors of ADAM17 against matrix metalloproteinase enzymes (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, and MMP-16) which have substantial structural similarity. Target proteins were docked with 29 anti-inflammatory natural molecule ligands and a known selective inhibitor IK682. The ligands were screened based on Lipinski rules, interaction with the ADAM17 active site cavity, and then ranked using the proportional odds model multinomial logistic regression.

Medicinal Chemistry and Drug Design (Cont'd)

A comparative study based on docking and molecular dynamics simulations over HDAC-tubulin dual inhibitors

Malihe Hassanzadeh, Kowsar Bagherzadeh, Massoud Amanlou [Tehran University of Medical Sciences]

J. Mol.Graph. and Mod., **69**, 170-180, 2016.

Nowadays the ability to prediction of complex behavior rationally based on the computational approaches has been a successful technique in drug discovery. In the present study interactions of a new series of hybrids, which were made by linking colchicine as a tubulin inhibitor and suberoylanilide hydroxamic acid (SAHA) as a HDAC inhibitor, with HDAC8 and HDAC1 were investigated and compared. This research has been facilitated by the availability of experimental information besides employing docking methodology as well as classical molecular dynamics simulations and binding free energy calculation were performed.

Transition-Tempered Metadynamics Is a Promising Tool for Studying the Permeation of Drug-like Molecules through Membranes

Rui Sun, James F. Dama, Jeffrey S. Tan, John P. Rose, and Gregory A. Voth [The University of Chicago]

J. Chem. Theor. and Comp., **12**, 5157–5169, 2016.

Metadynamics is an important enhanced sampling technique in molecular dynamics simulation to efficiently explore potential energy surfaces. The recently developed transition-tempered metadynamics (TTMetaD) has been proven to converge asymptotically without sacrificing exploration of the collective variable space in the early stages of simulations, unlike other convergent metadynamics (MetaD) methods. We have applied TTMetaD to study the permeation of drug-like molecules through a lipid bilayer to further investigate the usefulness of this method as applied to problems of relevance to medicinal chemistry.

Carbon Nanoparticles

The effect of protonation of cytosine and adenine on their interactions with carbon nanotubes

Marina V. Kosevich [University of Arizona, Tucson], Valentina G. Zobnina, Stepan G. Stepanian, Victor A. Karachevtsev, Ludwik Adamowicz

J. Mol.Graph. and Mod., **69**, 77-84, 2016.

Placing electrical charges on nanomaterials is a means to extend their functional capabilities in nanoelectronics and sensing applications. This paper explores the effect of charging nitrogen bases cytosine (Cyt) and adenine (Ade) via protonation on their noncovalent interaction with carbon nanotubes (CNT) using quantum chemical calculations performed at the M05-2X/6-31++G** level of theory alongside with a molecular graphics method. It is shown that the protonation of the bases causes threefold increase of the interaction energy in the CNT·Cyt·H⁺ and CNT·Ade·H⁺ complexes as compared to the CNT complexes formed with neutral bases.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Volume-rendering on a 3D hyperwall: A molecular visualization platform for research, education and outreach

Preston J. MacDougall, Christopher E. Henze, Anatoliy Volkov [Middle Tennessee State University]

J. Mol. Graph. and Mod., **69**, 1-6, 2016.

We present a unique platform for molecular visualization and design that uses novel subatomic feature detection software in tandem with 3D hyperwall visualization technology. We demonstrate the fleshing-out of pharmacophores in drug molecules, as well as reactive sites in catalysts, focusing on subatomic features. Topological analysis with picometer resolution, in conjunction with interactive volume-rendering of the Laplacian of the electronic charge density, leads to new insight into docking and catalysis.

Graphics Processing Unit Acceleration and Parallelization of GENESIS for Large-Scale Molecular Dynamics Simulations

Jaewoon Jung, Akira Nourse, Chigusa Kobayashi, and Yuji Sugita [RIKEN Theoretical Molecular Science Laboratory]

J. Chem. Theor. and Comp., **12**, 4947–4958, 2016.

The graphics processing unit (GPU) has become a popular computational platform for molecular dynamics (MD) simulations of biomolecules. A significant speedup in the simulations of small- or medium-size systems using only a few computer nodes with a single or multiple GPUs has been reported. Because of GPU memory limitation and slow communication between GPUs on different computer nodes, it is not straightforward to accelerate MD simulations of large biological systems that contain a few million or more atoms on massively parallel supercomputers with GPUs. In this study, we develop a new scheme in our MD software, GENESIS, to reduce the total computational time on such computers.

Dowser++, a new method of hydrating protein structures

A. Morozenko and A. A. Stuchebrukhov [University of California Davis]

Proteins: Stru. Fun. & Bioinf., **84**, 1347–1357, 2016.

A new method of hydrating protein structures, which we call Dowser++, is presented. The method is based on a semi-empirical modification of a popular program for protein hydration Dowser, and the usage of protocols AutoDock Vina, and WaterDock. The positions of water molecules predicted by Dowser++ were compared with experimental data for a set of 14 high-resolution crystal structures of oligopeptide-binding protein (OppA) containing a large number of resolved internal water molecules, as well as for the D- and K-channels of cytochrome c oxidase, and the recent data on PSII.

Artificial proteins as allosteric modulators of PDZ3 and SH3 in two-domain constructs: A computational characterization of novel chimeric proteins

Palani Kirubakaran, Lucie Pfeiferová, Kristýna Boušová, Lucie Bednarova, Veronika Obšilová and Jiří Vondrášek [Institute of Organic Chemistry and Biochemistry AS CR]

Proteins: Stru. Fun. & Bioinf., **84**, 1358–1374, 2016.

Artificial multidomain proteins with enhanced structural and functional properties can be utilized in a broad spectrum of applications. The design of chimeric fusion proteins utilizing protein domains or one-domain miniproteins as building blocks is an important advancement for the creation of new biomolecules for biotechnology and medical applications. Here, we tested an in silico design strategy using all-atom explicit solvent molecular dynamics simulations.

Bioinformatics and Cheminformatics (Cont'd)

FF12MC: A revised AMBER forcefield and new protein simulation protocol

Yuan-Ping Pang [Mayo Clinic, Rochester]

Proteins: Stru. Fun. & Bioinf., **84**, 1490–1516, 2016.

Specialized to simulate proteins in molecular dynamics (MD) simulations with explicit solvation, FF12MC is a combination of a new protein simulation protocol employing uniformly reduced atomic masses by tenfold and a revised AMBER forcefield FF99 with (i) shortened C H bonds, (ii) removal of torsions involving a nonperipheral sp³ atom, and (iii) reduced 1–4 interaction scaling factors of torsions ϕ and ψ .

Comparative or Homology Modeling

Structural and dynamic insights into the C-terminal extension of cysteine proteinase B from *Leishmania amazonensis*

Deborah Antunes Santos, Mauricio Garcia de Souza Costa, Carlos Roberto Alves, Ernesto Raul Caffarena [Programa De Computação Científica]

J. Mol.Graph. and Mod., **69**, 30-39, 2016.

Cysteine proteinase B (CPB) is a significant virulence factor for *Leishmania* infections. Upon processing from its zymogen form, it happens a release of the immunomodulatory CPB C-terminal extension (cyspep) into the cytoplasm of the macrophage. . Here, we attempted to build molecular models for this fragment and subsequently evaluate their stabilities in aqueous solution from molecular dynamics simulations analysis.

Protein Conformational Analysis

Intrinsically disordered regions stabilize the helical form of the C-terminal domain of RfaH: A molecular dynamics study

Sangni Xun, Fan Jiang, Yun-Dong Wu [Peking University Shenzhen Graduate School]

Bioorg. and Med. Chem., **24**, 4970-4977, 2016

RfaH protein functions as both transcription anti-terminator and translation enhancer in bacteria. Recent studies have shown that the C-terminal domain (CTD) is an α -helical hairpin (two-helix bundle) in full-length RfaH, despite the intrinsically favored β -barrel structure. Here, we carried out μ s-timescale molecular dynamics (MD) simulations for the wild-type (WT) RfaH, its E48S mutant and an established model without the intrinsically disordered region (IDR1) linking the CTD and the N-terminal domain (NTD).

Molecular dynamics-based investigation of InhA substrate binding loop for diverse biological activity of direct InhA inhibitors

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J. Biomol. Stru. And Dyn., **34**, 2434-2452, 2016.

The closed conformation of substrate binding loop (SBL) is considered significant for biological activity of direct InhA inhibitors (DIIs). However, exact interactions of SBL with inhibitors are not characterized yet to emphasize over SBL conformations. The seven InhA-DII complexes are analyzed using molecular dynamics simulation to deduce the mechanism for closed and open conformation of SBL. MMGBSA binding energy calculations and decompositions help to identify Ala198, Met199, Ile202, Val203, Ile215, and Leu218 in SBL region as the key residues.

Protein Conformational Analysis (Cont'd)

A molecular dynamics study of the BACE1 conformational change from Apo to closed form induced by hydroxyethylamine derived compounds

Carlos Gueto-Tettay, Joshua Zuchniarz, Yeyson Fortich-Seca, Luis Roberto Gueto-Tettay, Juan Carlos Drosos-Ramirez [Universidad de Cartagena]

J. Mol.Graph. and Mod., **69**, 181-195, 2016.

BACE1 is an aspartyl protease which is a therapeutic target for Alzheimer's disease (AD) because of its participation in the rate-limiting step in the production of A β -peptide, the accumulation of which produces senile plaques and, in turn, the neurodegenerative effects associated with AD. In the present study, comparative analysis of different combinations of protonation states for the BACE1-hydroxyethylamine (HEA) system is reported. HEAs are potent inhibitors of BACE1 with favorable pharmacological and kinetic properties, as well as oral bioavailability.

Using Dimensionality Reduction to Systematically Expand Conformational Sampling of Intrinsically Disordered Peptides

Oleksandra Kukharenko, Kevin Sawade, Jakob Steuer, and Christine Peter [University of Konstanz]

J. Chem. Theor. and Comp, **12**, 4726–4734, 2016.

One of the approaches to improve our ability to characterize biologically important processes and to map out an underlying free energy landscape is to direct MD simulations to explore molecular conformational phase space faster. Intrinsically disordered systems with shallow free energy landscapes of a huge number of metastable minima pose a particular challenge in this regard. We have used a multidimensional scaling-like embedding (sketch-map) to describe the energetically accessible regions of phase space for a peptide fragment of the intrinsically disordered protein α -synuclein.

Does Replica Exchange with Solute Tempering Efficiently Sample A β Peptide Conformational Ensembles?

Amy K. Smith, Christopher Lockhart, and Dmitri K. Klimov [George Mason University, Manassas]

J. Chem. Theor. and Comp, **12**, 5201–5214, 2016.

We have applied replica exchange with solute tempering (REST) molecular dynamics to study a short fragment of the A β peptide, A β 25-35, in water and a much larger system incorporating two A β 10-40 peptides binding to the zwitterionic dimyristoylphosphatidylcholine (DMPC) bilayer. As a control, we used traditional replica exchange molecular dynamics (REMD) applied to the same systems. Our objective was to assess the practical utility of REST simulations. Taken together, our results suggest four conclusions.

Extraction of Protein Conformational Modes from Distance Distributions Using Structurally Imputed Bayesian Data Augmentation

Xun Sun, Thomas E. Morrell, and Haw Yang [Princeton University, Princeton]

J. Phys. Chem. B., **120**, 10469–10482, 2016.

Protein conformational changes are known to play important roles in assorted biochemical and biological processes. Driven by thermal motions of surrounding solvent molecules, such a structural remodeling often occurs stochastically. Yet, regardless of how random the conformational reconfiguration may appear, it could in principle be described by a linear combination of a set of orthogonal modes which, in turn, are contained in the intramolecular distance distributions. The central challenge is how to obtain the distribution.

Protein Conformational Analysis (Cont'd)

Conformational Change in the Mechanism of Inclusion of Ketoprofen in β -Cyclodextrin: NMR Spectroscopy, Ab Initio Calculations, Molecular Dynamics Simulations, and Photoreactivity

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J. Phys. Chem. B., **120**, 10668–10678, 2016.

Inclusion of drugs in cyclodextrins (CDs) is a recognized tool for modifying several properties such as solubility, stability, bioavailability, and so on. The photoreactive behavior of the β -CD/ketoprofen (KP) complex upon UV exposure showed a significant increase in photodecarboxylation, whereas the secondary degradation products by hydroxylation of the benzophenone moiety were inhibited. The results may account for an improvement of KP photophysical properties upon inclusion, thus better fostering its topical use. To correlate the structural details of the inclusion with these results, an NMR spectroscopic study of KP upon inclusion in β -CD was performed.

Protein Structure Analysis

3D structure prediction of histone acetyltransferase proteins of the MYST family and their interactome in *Arabidopsis thaliana*

A. V. Raevsky [National Academy of Sciences of Ukraine], M. Sharifi, D. A. Samofalova, P. A. Karpov, Y. B. Blume

J. Mol.Mod., **22**, 256, 2016.

Histone lysine acetylation is a reversible post-translational modification that does not involve changes in DNA sequences. Enzymes play an important role in developmental processes and their deregulation has been linked to the progression of diverse disorders. The HAT enzyme family fulfills an important role in various developmental processes mediated by the state of chromatin, and have been attributed to its deregulation. To understand acetylation mechanisms and their role in cell signaling, transcriptional regulation, and apoptosis, it is crucial to identify and analyze acetylation sites.

Protein Dynamics

Enhancing backbone sampling in Monte Carlo simulations using internal coordinates normal mode analysis

Victor A. Gil [Barcelona Supercomputing Center], Daniel Lecina, Christoph Grebner, Victor Guallar

Bioorg. and Med. Chem., **24**, 4855–4866, 2016

Normal mode methods are becoming a popular alternative to sample the conformational landscape of proteins. In this study, we describe the implementation of an internal coordinate normal mode analysis method and its application in exploring protein flexibility by using the Monte Carlo method PELE. This new method alternates two different stages, a perturbation of the backbone through the application of torsional normal modes, and a resampling of the side chains.

Protein Dynamics (Cont'd)

Electric Field Keeps Chromophore Planar and Produces High Yield Fluorescence in Green Fluorescent Protein

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J. Am. Chem. Soc., **138**, 13619–13629, 2016.

The green fluorescent protein and its designed variants fluoresce efficiently. Because the isolated chromophore is not fluorescent in a practical sense, it is apparent that the protein environment plays a crucial role in its efficiency. Because of various obstacles in studying excited state dynamics of complex systems, however, the detailed mechanism of this efficiency enhancement is not yet clearly elucidated. Here, by adopting excited state nonadiabatic molecular dynamics simulations together with an interpolated quantum chemical potential model of the chromophore, we find that the strong electric field from the protein matrix contributes dominantly to the motional restriction of the chromophore.

A pH-dependent computational approach to the effect of mutations on protein stability

Velin Z. Spasov [BIOVIA, Dassault Systemes] and Lisa Yan

J. Comp. Chem., **37**, 2573–2587, 2016.

This article describes a novel software implementation for high-throughput scanning mutagenesis with a focus on protein stability. The approach combines molecular mechanics calculations with calculations of protein ionization and a Gaussian-chain model of electrostatic interactions in unfolded state. Comprehensive testing demonstrates a state-of-the-art accuracy for predicted free energy differences on single, double, and triple mutations with a correlation coefficient R above 0.7, which takes about 1.5 min per mutation on a single CPU.

pH-controlled doxorubicin anticancer loading and release from carbon nanotube noncovalently modified by chitosan: MD simulations

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J. Mol. Graph. and Mod., **69**, 70–76, 2016.

In the present study, we describe here the pH condition activating doxorubicin (DOX) anticancer drugs loading and release over single-wall carbon nanotube (SWNT) non-covalently wrapped with chitosan (CS). The possibility of drug displacement on DOX/CS/SWNT nanocarrier was investigated using molecular dynamics simulations. The drug loading and release were monitored via displacement analysis and binding energy calculations.

Multi scale modeling of 2450 MHz electric field effects on microtubule mechanical properties

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J. Mol. Graph. and Mod., **69**, 122–128, 2016.

Microtubule (MT) rigidity and response to 2450 MHz electric fields were investigated, via multi scale modeling approach. For this purpose, six systems were designed and simulated to consider all types of feasible interactions between α and β monomers in MT, by using all atom molecular dynamics method. Subsequently, coarse grain modeling was used to design different lengths of MT. Investigation of effects of external 2450 MHz electric field on MT showed MT less rigidity in the presence of such field, which may perturb its functions.

Protein Dynamics (Cont'd)

Protein remains stable at unusually high temperatures when solvated in aqueous mixtures of amino acid based ionic liquids

Guillaume Chevrot, Eudes Eterno Fileti [Universidade Federal de São Paulo], Vitaly V. Chaban

J. Mol.Mod., **22**, 258, 2016.

Using molecular dynamics simulations, we investigated the thermal stability and real-time denaturation of a model mini-protein in four solvents: (1) water, (2) 1-ethyl-3-methylimidazolium alaninate [EMIM][ALA] (5 mol% in water), (3) methioninate [EMIM][MET] (5 mol% in water), and (4) tryptophanate [EMIM][TRP] (5 mol% in water). Upon analyzing the radius of gyration, the solvent-accessible surface area, root-mean-squared deviations, and inter- and intramolecular hydrogen bonds, we found that the mini-protein remains stable at 30–40 K higher temperatures in aqueous amino acid based ionic liquids (AAILs) than in water.

In silico study of amphiphilic nanotubes based on cyclic peptides in polar and non-polar solvent

Vinodhkumar Vijayakumar, Ramadoss Vijayaraj, Günther H. Peters [Technical University of Denmark]

J. Mol.Mod., **22**, 264, 2016.

The stability of cyclic peptide assemblies (CPs) forming a macromolecular nanotube structure was investigated in solvents of different polarity using computational methods. The stability and structure of the complexes were studied using traditional molecular dynamics (MD). Energy of dissociation was estimated from steered MD in combination with umbrella sampling simulations. A cyclic peptide nanotube (CPNT) was constructed by stacking of eight cyclo[(d-Trp-l-Gln-d-Trp-l-Glu)₂], and hereafter is referred to as (WQWE)₈. Its dissociation was studied by pulling 1, 2, or 3 subunits from the nanotube.

Ligand Binding/Docking

AutoSite: an automated approach for pseudo-ligands prediction—from ligand-binding sites identification to predicting key ligand atoms

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Bioinformatics. **32**, 3142-3149, 2016.

The identification of ligand-binding sites from a protein structure facilitates computational drug design and optimization, and protein function assignment. We introduce AutoSite: an efficient software tool for identifying ligand-binding sites and predicting pseudo ligand corresponding to each binding site identified. We show that AutoSite identifies ligand-binding sites with higher accuracy than other leading methods, and produces fills that better matches the ligand shape and properties, than the fills obtained with a software program with similar capabilities, AutoLigand.

Parametrization of halogen bonds in the CHARMM general force field: Improved treatment of ligand–protein interactions

Ignacio Soteras Gutiérrez, Fang-Yu Lin, Kenno Vanommeslaeghe, Justin A. Lemkul, Kira A. Armacost, Charles L. Brooks III, Alexander D. MacKerell Jr. [University of Maryland, Baltimore]

Bioorg. and Med. Chem., **24**, 4812-4825, 2016

A halogen bond is a highly directional, non-covalent interaction between a halogen atom and another electronegative atom. It arises due to the formation of a small region of positive electrostatic potential opposite the covalent bond to the halogen, called the ‘sigma hole’. A strategy to overcome this problem is to attach a positively charged virtual particle to the halogen. In this work, we extend the additive CHARMM General Force Field (CGenFF) to include such interactions in model systems of phenyl-X, with X being Cl, Br or I including di- and trihalogenated species.

Ligand Binding / Docking (Cont'd)

Blinded predictions of binding modes and energies of HSP90- α ligands for the 2015 D3R grand challenge

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Bioorg. and Med. Chem., **24**, 4890-4899, 2016

In the framework of the 2015 D3R inaugural grand challenge, blind binding pose and affinity predictions were performed for a set of 180 ligands of the Heat Shock Protein HSP90- α protein, a relevant cancer target. Spectral clustering was used to rapidly identify alternative binding site conformations in publicly available crystallographic HSP90- α structures. Subsequently, multiple docking and scoring protocols employing the software Autodock Vina and rDock were applied to predict binding modes and rank order ligands.

Exploring the interaction between human focal adhesion kinase and inhibitors: a molecular dynamic simulation and free energy calculations

Jiu-Yu Zhan, Ji-Long Zhang, Yan Wang, Ye Li, Hong-Xing Zhang & Qing-Chuan Zheng [Jilin University, Changchun]

J. Biomol. Stru. And Dyn., **34**, 2351-2366, 2016.

Focal adhesion kinase is an important target for the treatment of many kinds of cancers. Inhibitors of FAK are proposed to be the anticancer agents for multiple tumors. The interaction characteristic between FAK and its inhibitors is crucial to develop new inhibitors. In the present article, we used Molecular Dynamic (MD) simulation method to explore the characteristic of interaction between FAK and three inhibitors (PHM16, TAE226, and ligand3). The MD simulation results together with MM-GB/SA calculations show that the combinations are enthalpy-driven process.

Molecular simulations of lactose-bound and unbound forms of the FaeG adhesin reveal critical amino acids involved in sugar binding

Joseph L. Baker [The College of New Jersey], Heba Jafri

J. Mol.Graph. and Mod., **69**, 100-108, 2016.

F4 fimbriae are protein filaments found in enterotoxigenic Escherichia coli cells and are implicated in the process of bacterial infection due to their function as bacterial adhesins. These filaments are comprised from several proteins, but the bacterial adhesin FaeG, which is a lactose-binding protein, is the major subunit comprising F4 fimbriae. However, the dynamics of the FaeG protein bound to lactose have not been explored previously using molecular dynamics simulations. Therefore, in order to study the dynamical interactions between the FaeG ad variant and lactose, we have carried out the first all-atom molecular dynamics simulations of this system.

Integration of ligand and structure based approaches for identification of novel MbtI inhibitors in Mycobacterium tuberculosis and molecular dynamics simulation studies

Lakshmi Maganti, Pradeep Grandhi, Nanda Ghoshal [CSIR-Indian Institute of Chemical Biology]

J. Mol.Graph. and Mod., **69**, 14-22, 2016.

Mycobacterium tuberculosis is an obligate pathogen of mammals and is responsible for more than two million deaths annually. The ability to acquire iron from the extracellular environment is a key determinant of pathogenicity in mycobacteria. M. tuberculosis acquires iron exclusively through the siderophores. Hence, in the present study, we have used a combined ligand and structure-based drug design approach for identification of novel inhibitors against salicylate synthase MbtI, a unique and essential enzyme for the biosynthesis of siderophores in M. tuberculosis.

Ligand Binding / Docking (Cont'd)

Molecular design and validation of halogen bonding orthogonal to hydrogen bonding in breast cancer MDM2–peptide complex

Anzhong Huang, Liang Zhou [Jinshan Hospital, Fudan University], Dawei Zhang, Junliang Yao, Yong Zhang

J. Mol.Graph. and Mod., **69**, 40-44, 2016.

Peptide therapeutics has been raised as an attractive approach for the treatment of breast cancer by targeting the oncogenic protein MDM2 that inactivates p53 tumor suppressor. Here, we performed molecular design of halogen bonding orthogonal to hydrogen bonding at the complex interface of MDM2 protein with its cognate peptide ligand to improve the peptide binding affinity and specificity.

Molecular simulation study of the unbinding of α -conotoxin [Y4E]GID at the $\alpha 7$ and $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors

Abishek Suresh, Andrew Hung [School of Science, RMIT University]

J. Mol.Graph. and Mod., **69**, 109-121, 2016.

The $\alpha 7$ and $\alpha 4\beta 2$ neuronal nicotinic receptors belonging to the family of ligand-gated ion channels are most prevalent in the brain, and are implicated in various neurodegenerative disorders. α -conotoxin GID (and its analogue [Y4E]GID) specifically inhibits these subtypes, with more affinity towards the human $\alpha 7$ ($h\alpha 7$) subtype, and is valuable in understanding the physiological roles of these receptors. In this study, we use umbrella-sampling molecular dynamics simulations to understand the mechanism of interaction between [Y4E]GID and the agonist binding pockets of the $\alpha 4\beta 2$ and the $h\alpha 7$ receptors, and to estimate their relative binding affinities (ΔG_{bind}).

Effect of allosteric molecules on structure and drug affinity of HIV-1 protease by molecular dynamics simulations

Xian-Mei Meng, Wei-Jun Hu, Yu-Guang Mu [Nanyang Technological University], Xie-Huang Sheng

J. Mol.Graph. and Mod., **69**, 153-162, 2016.

Recent experiments show that small molecules can bind onto the allosteric sites of HIV-1 protease (PR), which provides a starting point for developing allosteric inhibitors. However, the knowledge of the effect of such binding on the structural dynamics and binding free energy of the active site inhibitor and PR is still lacking. Here, we report 200 ns long molecular dynamics simulation results to gain insight into the influences of two allosteric molecules (1H-indole-6-carboxylic acid, 1F1 and 2-methylcyclohexano, 4D9).

Molecular Mechanisms of the Bindings between Non-Amyloid β Component Oligomers and Amylin Oligomers

Yoav Atsmon-Raz and Yifat Miller [Ben-Gurion University of the Negev]

J. Phys. Chem. B., **120**, 10649–10659, 2016.

It has been suggested that the connection between amyloidogenic diseases is related to the interactions between aggregates of amyloids, which are related to type 2 diabetes and Parkinson's disease. Herein, we illustrate the interactions between amylin oligomers and non-amyloid β component (NAC) oligomers. Using molecular dynamics simulations and statistical calculations, we studied the mechanisms through which NAC oligomers interact with amylin oligomers to form NAC–amylin hetero-oligomers.

Ligand Binding / Docking (Cont'd)

The binding affinity of human serum albumin and paclitaxel through MMPBSA based on docked complex

Huaxing Yu, Daixi Li [University of Shanghai for Science and Technology], Fei Xu, Qi Pan, Pei Chai, Baolin Liu & Chenglung Chen

Molec. Simul., **42**, 1460-1467, 2016.

The distribution, free concentration and metabolism of drugs can be significantly altered as a result of binding to albumin. At the same time, the conformational of serum albumin was also changed by interaction with low molecular weight drugs. In present work, we first equilibrated HSA in aqueous solution to obtain the solvated-HSA model. Further solvated-HSA was performed molecular docking with paclitaxel to find the binding sites. The two docking HSA-paclitaxel complexes were obtained and further equilibrated by a 12 ns MD simulation.

BiPPred: Combined sequence- and structure-based prediction of peptide binding to the Hsp70 chaperone BiP

Markus Schneider, Mathias Rosam, Manuel Glaser, Atanas Patronov, Harpreet Shah, Katrin Christiane Back, Marina Angelika Daake, Johannes Buchner and Iris Antes [Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **84**, 1390–1407, 2016.

Substrate binding to Hsp70 chaperones is involved in many biological processes, and the identification of potential substrates is important for a comprehensive understanding of these events. We present a multi-scale pipeline for an accurate, yet efficient prediction of peptides binding to the Hsp70 chaperone BiP by combining sequence-based prediction with molecular docking and MMPBSA calculations. First, we measured the binding of 15mer peptides from known substrate proteins of BiP by peptide array (PA) experiments and performed an accuracy assessment of the PA data by fluorescence anisotropy studies.

Accelerated molecular dynamics simulations of the octopamine receptor using GPUs: discovery of an alternate agonist-binding position

Kevin W. Kastner and Jesús A. Izaguirre [University of Notre Dame, Notre Dame]

Proteins: Stru. Fun. & Bioinf., **84**, 1480–1489, 2016.

Octopamine receptors (OARs) perform key biological functions in invertebrates, making this class of G-protein coupled receptors (GPCRs) worth considering for insecticide development. However, no crystal structures and very little research exists for OARs. Furthermore, GPCRs are large proteins, are suspended in a lipid bilayer, and are activated on the millisecond timescale, all of which make conventional molecular dynamics (MD) simulations infeasible, even if run on large supercomputers.

Enzyme Catalysis

Understanding protein arginine methyltransferase 1 (PRMT1) product specificity from molecular dynamics

Symon Gathiaka, Brittany Boykin, Tamar Cáceres, Joan M. Hevel, Orlando Acevedo [University of Miami, Coral Gables]

Bioorg. and Med. Chem., **24**, 4949-4960, 2016

Protein arginine methyltransferases (PRMTs) catalyze the post-translational methylation of specific arginyl groups within targeted proteins to regulate fundamental biological responses in eukaryotic cells. The major Type I PRMT enzyme, PRMT1, strictly generates monomethyl arginine (MMA) and asymmetric dimethylarginine (ADMA), but not symmetric dimethylarginine (SDMA). Multiple diseases can arise from the dysregulation of PRMT1, including heart disease and cancer, which underscores the need to elucidate the origin of product specificity. Molecular dynamics (MD) simulations were carried out for WT PRMT1 and its M48F, H293A, H293S, and H293S-M48F mutants bound with S-adenosylmethionine (AdoMet) and the arginine substrate in an unmethylated or methylated form.

Dual anti-inflammatory and selective inhibition mechanism of leukotriene A4 hydrolase/aminopeptidase: insights from comparative molecular dynamics and binding free energy analyses

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J. Biomol. Stru. And Dyn., **34**, 2418-2433, 2016.

Human leukotriene A4 hydrolase/aminopeptidase (LTA4H) is a zinc metalloenzyme with a dual catalytic activity; conversion of LTA4 into LTB4 and degradation of chemotactic tripeptide Pro-Gly-Pro (PGP). Existing inhibitors, such as SC-57461A, block both catalytic activities of the enzyme, leading to drug failures. We embarked on wide range of computational tools, including comparative molecular dynamics (MDs) simulations and postdynamic analyses for LTA4H and in complex with ARM1, PGP, ARM1-PGP, and SC-57461A.

Mutated form (G52E) of inactive diphtheria toxin CRM197: molecular simulations clearly display effect of the mutation to NAD binding

Ramin Ekhteiri Salmas, Mert Mestanoglu, Ayhan Unlu, Mine Yurtsever & Serdar Durdagi [Bahcesehir University]

J. Biomol. Stru. And Dyn., **34**, 2462-2468, 2016.

Mutated form (G52E) of diphtheria toxin (DT) CRM197 is an inactive and nontoxic enzyme. Here, we provided a molecular insight using comparative molecular dynamics (MD) simulations to clarify the influence of a single point mutation on overall protein and active-site loop. Post-processing MD analysis (i.e. stability, principal component analysis, hydrogen-bond occupancy, etc.) is carried out on both wild and mutated targets to investigate and to better understand the mechanistic differences of structural and dynamical properties on an atomic scale especially at nicotinamide adenine dinucleotide (NAD) binding site when a single mutation (G52E) happens at the DT.

Insights into the spontaneity of hydrogen bond formation between formic acid and phthalimide derivatives

Rogério V. A. Júnior, Gustavo L. C. Moura, Nathalia B. D. Lima [Universidade Federal de Pernambuco]

J. Mol.Mod., **22**, 255, 2016.

A new method for predicting the energy contributions to substrate binding and to specificity has been developed. Conventional global optimization methods do not permit the subtle effects responsible for these properties to be modeled with sufficient precision to allow confidence to be placed in the results, but by making simple alterations to the model, the precisions of the various energies involved can be improved from about ± 2 kcal mol⁻¹ to ± 0.1 kcal mol⁻¹.

Enzyme Catalysis (Cont'd)

Beware of Unreliable Q2! A Comparative Study of Regression Metrics for Predictivity Assessment of QSAR Models

Roberto Todeschini [University of Milano-Bicocca], Davide Ballabio, and Francesca Grisoni

J.Chem. Infor. and Mod., **56**, 1905–1913, 2016.

In silico virtual screening (VS) is a powerful hit identification technique used in drug discovery projects that aims to effectively distinguish true actives from inactive or decoy molecules. To better capture the dynamic behavior of protein drug targets, compound databases may be screened against an ensemble of protein conformations, which may be experimentally determined or generated computationally, i.e. via molecular dynamics (MD) simulations. We assess whether MD conformations result in improved VS performance for six protein kinases.

A Semiautomated Structure-Based Method To Predict Substrates of Enzymes via Molecular Docking: A Case Study with *Candida antarctica* Lipase B

Zhiqiang Yao, Lujia Zhang, Bei Gao, Dongbing Cui, Fengqing Wang, Xiao He, John Z. H. Zhang, and Dongzhi Wei [East China University of Science and Technology]

J.Chem. Infor. and Mod., **56**, 1979–1994, 2016.

The discovery of unique substrates is important for developing potential applications of enzymes. However, the experimental procedures for substrate identification are laborious, time-consuming, and expensive. Here we present an open-source, extensible, and flexible software platform for predicting enzyme substrates called THEMIS, which performs in silico virtual screening for potential catalytic targets of an enzyme on the basis of the enzyme's catalysis mechanism.

Structural Basis of Fullerene Derivatives as Novel Potent Inhibitors of Protein Tyrosine Phosphatase 1B: Insight into the Inhibitory Mechanism through Molecular Modeling Studies

Mengdan Qian, Yaming Shan, Shanshan Guan, Hao Zhang, Song Wang, and Weiwei Han [Jilin University]

J.Chem. Infor. and Mod., **56**, 2024–2034, 2016.

Protein tyrosine phosphatase 1B (PTP1B) has become an outstanding target for the treatment of diabetes and obesity. Recent research has demonstrated that some fullerene derivatives serve as a new nanoscale-class of potent inhibitors of PTP1B, but the specific mechanism remains unclear. Several molecular modeling methods (molecular docking, molecular dynamics simulations, and molecular mechanics/generalized Born surface area calculations) were integrated to provide insight into the binding mode and inhibitory mechanism of the new class of fullerene inhibitors.

Theoretical Investigation of the Mechanisms of ERK2 Enzymatic Catalysis

Mikita M. Misiura and Anatoly B. Kolomeisky [Rice University, Houston]

J. Phys. Chem. B., **120**, 10508–10514, 2016.

ERK2 are protein kinases that during the enzymatic catalysis, in contrast to traditional enzymes, utilize additional interactions with substrates outside of the active sites. It is widely believed that these docking interactions outside of the enzymatic pockets enhance the specificity of these proteins. However, the molecular mechanisms of how the docking interactions affect the catalysis remain not well understood. Here, we develop a simple theoretical approach to analyze the enzymatic catalysis in ERK2 proteins.

Enzyme Catalysis (Cont'd)

Computational exploration of the binding mode of heme-dependent stimulators into the active catalytic domain of soluble guanylate cyclase

Luis Agulló [University of Vic – Central University of Catalonia], Ignasi Buch, Hugo Gutiérrez-de-Terán, David García-Dorado and Jordi Villà-Freixa

Proteins: Stru. Fun. & Bioinf., **84**, 1534–1548, 2016.

Soluble guanylate cyclase (sGC), the main target of nitric oxide (NO), has been proven to have a significant role in coronary artery disease, pulmonary hypertension, erectile dysfunction, and myocardial infarction. One of its agonists, BAY 41-2272 (Riociguat), has been recently approved for treatment of pulmonary arterial hypertension (PHA), while some others are in clinical phases of development. However, the location of the binding sites for the two known types of agonists, heme-dependent stimulators and heme-independent activators, is a matter of debate. Here, we address its potential location on the catalytic domain, the unique well characterized at the structural level, by an “in silico” approach.

Protein-Protein Interactions

Analysis of Loops that Mediate Protein-Protein Interactions and Translation into Submicromolar Inhibitors

Timothy R. Siegert, Michael J. Bird, Kamlesh M. Makwana, and Joshua A. Kritzer [Tufts University]

J. Am. Chem. Soc., **138**, 12876–12884, 2016.

Effective strategies for mimicking α -helix and β -strand epitopes have been developed, producing valuable inhibitors for some classes of protein-protein interactions (PPIs). However, there are no general strategies for translating loop epitopes into useful PPI inhibitors. In this work, we use the LoopFinder program to identify diverse sets of “hot loops,” which are loop epitopes that mediate PPIs. These include loops that are well-suited to mimicry with macrocyclic compounds, and loops that are most similar to variable loops on antibodies and ankyrin repeat proteins.

Model Building of Antibody-Antigen Complex Structures Using GBSA Scores

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J. Chem. Infor. and Mod., **56**, 2005–2012, 2016.

Structure prediction of antibody-antigen complexes, which involves molecular docking to generate decoys that are ranked using a scoring function, is an important approach in the design of antibody drugs and biosensors. However, it is not easy to evaluate the stability of protein-protein complexes, using a single scoring function. Here, we developed a prediction method of antibody-antigen complex structures using the docking engine “surFit” and a scoring function (GBSA score) that combined the generalized Born (GB) energy and the hydration energy based on the solvent-accessible surface area (SA).

Membrane Proteins and Lipid Peptide Interactions

Insights into membrane translocation of the cell-penetrating peptide pVEC from molecular dynamics calculations

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[Bogazici University, Bebek]

J. Biomol. Stru. And Dyn., **34**, 2387-2398, 2016.

Discovery of cargo carrying cell-penetrating peptides has opened a new gate in the development of peptide-based drugs that can effectively target intracellular enzymes. Success in application and development of cell-penetrating peptides in drug design depends on understanding their translocation mechanisms. In this study, our aim was to examine the bacterial translocation mechanism of the cell-penetrating pVEC peptide (LLIILRRRIRKQAHASK) using steered molecular dynamics (SMD) simulations.

Molecular simulation study on concentration effects of rofecoxib with POPC bilayer

Huanjie Wang, Fancui Meng [Tianjin Institute of Pharmaceutical Research]

J. Mol.Graph. and Mod., **69**, 94-99, 2016.

The interactions between rofecoxib and POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) bilayer were studied using all-atom molecular dynamics simulation method. Four POPC bilayer systems with different number of rofecoxib molecules were constructed to simulate different drug concentration. The free energy of rofecoxib passing across pure POPC bilayer has two minima (at $z \sim 1.2$ nm or 1.6 nm). As for the high concentration model, the minimum of the free energy profile slightly shifts to the bilayer center.

Passive Transmembrane Permeation Mechanisms of Monovalent Ions Explored by Molecular Dynamics Simulations

Hui-Yuan Zhang, Qin Xu, Yu-Kun Wang, Tang-Zhen Zhao, Dan Hu, and Dong-Qing Wei [Shanghai Jiao Tong University]

J. Chem. Theor. and Comp., **12**, 4959–4969, 2016.

Passive or unassisted ion permeation through lipid bilayers involves a type of rare events by which cells regulate their salt concentrations and pH. It is important to understand its mechanism in order to develop technologies of, for example, delivering or maintaining small drug-like molecules inside cells. In this work, this technique was used to study the permeation processes of some well-known ions, sodium, potassium, and chloride. It is found permeations of sodium and potassium are assisted by important lipid bilayer deformations and massive water solvation, while chloride may not.

Biological Membranes in Extreme Conditions: Anionic Tetraether Lipid Membranes and Their Interactions with Sodium and Potassium

Luis Felipe Pineda De Castro, Mark Dopson, and Ran Friedman [Linnæus University]

J. Phys. Chem. B., **120**, 10628–10634, 2016.

Archaea such as *Sulfolobus acidocaldarius* tolerate extreme temperatures and high acidity and can grow in the presence of toxic metals and low concentrations of Na^+ or K^+ . It is believed that their unique tetraether membranes protect them from harsh environments and allow their survival under such conditions. We used molecular dynamics simulations to study membranes comprising glycerol dialkylnonitol tetraether lipids, which are the main component of *S. acidocaldarius* membranes, in solutions containing different concentrations of NaCl and KCl or with Na^+ or K^+ counterions (trace cations, 0 M).

Protein Folding

Sensitivity of Folding Molecular Dynamics Simulations to Even Minor Force Field Changes

Athanasia-Panagiota Serafeim, Georgios Salamanos, Kalliopi K. Patapati, and Nicholas M. Glykos [Democritus University of Thrace]

J.Chem. Infor. and Mod., **56**, 2035–2041, 2016.

We examine the sensitivity of folding molecular dynamics simulations on the choice between three variants of the same force field (the AMBER99SB force field and its ILDN, NMR-ILDN, and STAR-ILDN variants). Using two different peptide systems (a marginally stable helical peptide and a β -hairpin) and a grand total of more than 20 μ s of simulation time we show that even relatively minor force field changes can lead to appreciable differences in the peptide folding behavior.

Protein-Nucleic acid Interactions

Molecular Mechanism of Facilitated Dissociation of Fis Protein from DNA

Min-Yeh Tsai, Bin Zhang, Weihua Zheng, and Peter G. Wolynes [Rice University, Houston]

J. Am. Chem. Soc., **138**, 13497–13500, 2016.

Fis protein is a nucleoid-associated protein that plays many roles in transcriptional regulation and DNA site-specific recombination. In contrast to the naïve expectation based on stoichiometry, recent single-molecule studies have shown that the dissociation of Fis protein from DNA is accelerated by increasing the concentration of the Fis protein. Because the detailed molecular mechanism of facilitated dissociation is still not clear, in this study, we employ computational methods to explore the binding landscapes of Fis:DNA complexes with various stoichiometries.

Binding of Telomestatin to a Telomeric G-Quadruplex DNA Probed by All-Atom Molecular Dynamics Simulations with Explicit Solvent

Kelly Mulholland and Chun Wu [Rowan University, Glassboro]

J.Chem. Infor. and Mod., **56**, 2093–2102, 2016.

Telomestatin, a natural product isolated from *Streptomyces anulatus*, stabilizes telomeric DNA G-quadruplexes. Treatment with this ligand induces apoptosis of various cancer cells with a relatively low effect on somatic cells because of its high selectivity toward G-quadruplex over duplex DNA. A high-resolution structure of a G-quadruplex in complex with telomestatin does not yet exist because of its low solubility, and the binding nature of this ligand remains elusive. In this study, we utilized molecular binding simulations and MMGBSA binding energy analysis to decipher the nature of the binding of telomestatin to a telomeric G-quadruplex.

Enhanced Dynamics of Hydrated tRNA on Nanodiamond Surfaces: A Combined Neutron Scattering and MD Simulation Study

Gurpreet K. Dhindsa, Debsindhu Bhowmik, Monojoy Goswami, Hugh O'Neill, Eugene Mamontov, Bobby G. Sumpter, Liang Hong, Panchapakesan Ganesh, and Xiang-qiang Chu [Wayne State University, Detroit]

J. Phys. Chem. B., **120**, 10059–10068, 2016.

Nontoxic, biocompatible nanodiamonds (ND) have recently been implemented in rational, systematic design of optimal therapeutic use in nanomedicines. However, hydrophilicity of the ND surface strongly influences structure and dynamics of biomolecules that restrict in situ applications of ND. Therefore, fundamental understanding of the impact of hydrophilic ND surface on biomolecules at the molecular level is essential. For tRNA, we observe an enhancement of dynamical behavior in the presence of ND contrary to generally observed slow motion at strongly interacting interfaces.

Nucleic Acids

Prediction of conserved long-range RNA-RNA interactions in full viral genomes

Markus Fricke and Manja Marz [Friedrich Schiller University Jena]

Bioinformatics. **32**, 2928-2935, 2016.

Long-range RNA-RNA interactions (LRIs) play an important role in viral replication, however, only a few of these interactions are known and only for a small number of viral species. We present LRIsScan, a tool for the LRI prediction in full viral genomes based on a multiple genome alignment. We confirmed 14 out of 16 experimentally known and evolutionary conserved LRIs in genome alignments of HCV, Tombusviruses, Flaviviruses and HIV-1. We provide several promising new interactions, which include compensatory mutations and are highly conserved in all considered viral sequences.

Large-Scale Conformational Transitions in Supercoiled DNA Revealed by Coarse-Grained Simulation

Brad A. Krajina, Andrew J. Spakowitz [Stanford University]

Biophysical Journal., **111**, 1339-1349, 2016.

Topological constraints, such as those associated with DNA supercoiling, play an integral role in genomic regulation and organization in living systems. However, physical understanding of the principles that underlie DNA organization at biologically relevant length scales remains a formidable challenge. We develop a coarse-grained simulation approach for predicting equilibrium conformations of supercoiled DNA. Our methodology enables the study of supercoiled DNA molecules at greater length scales and supercoiling densities than previously explored by simulation.

Monte Carlo simulation algorithm for B-DNA

Steven C. Howell, Xiangyun Qiu and Joseph E. Curtis [NIST Center for Neutron Research]

J. Comp. Chem., **37**, 2553–2563, 2016.

Understanding the structure–function relationship of biomolecules containing DNA has motivated experiments aimed at determining molecular structure using methods such as small-angle X-ray and neutron scattering (SAXS and SANS). SAXS and SANS are useful for determining macromolecular shape in solution, a process which benefits by using atomistic models that reproduce the scattering data. The variety of algorithms available for creating and modifying model DNA structures lack the ability to rapidly modify all-atom models to generate structure ensembles.

Computational Approach for Studying Optical Properties of DNA Systems in Solution

Morten Steen Nørby [University of Southern Denmark], Casper Steinmann, Jógvan Magnus

J. Chem. Theor. and Comp, **12**, 5050–5057, 2016.

In this paper we present a study of the methodological aspects regarding calculations of optical properties for DNA systems in solution. Our computational approach will be built upon a fully polarizable QM/MM/Continuum model within a damped linear response theory framework. In this approach the environment is given a highly advanced description in terms of the electrostatic potential through the polarizable embedding model. Furthermore, bulk solvent effects are included in an efficient manner through a conductor-like screening model.

2. METHODOLOGY

Quantitative Structure-Activity Relations

A DFT-based QSAR study on inhibition of human dihydrofolate reductase

Sedat Karabulut [Balikesir University, Balikesir], Natalia Sizochenko, Adnan Orhan, Jerzy Leszczynski

J. Mol. Graph. and Mod., **69**, 23-29, 2016.

Diaminopyrimidine derivatives are frequently used as inhibitors of human dihydrofolate reductase, for example in treatment of patients whose immune system are affected by human immunodeficiency virus. Forty-seven dicyclic and tricyclic potential inhibitors of human dihydrofolate reductase were analyzed using the quantitative structure-activity analysis supported by DFT-based and DRAGON-based descriptors. The developed model yielded an RMSE deviation of 1.1 a correlation coefficient of 0.81.

Beware of Unreliable Q2! A Comparative Study of Regression Metrics for Predictivity Assessment of QSAR Models

Roberto Todeschini [University of Milano-Bicocca], Davide Ballabio, and Francesca Grisoni

J. Chem. Infor. and Mod., **56**, 1905–1913, 2016.

Validation is an essential step of QSAR modeling, and it can be performed by both internal validation techniques (e.g., cross-validation, bootstrap) or by an external set of test objects, that is, objects not used for model development and/or optimization. The evaluation of model predictive ability is then completed by comparing experimental and predicted values of test molecules. When dealing with quantitative QSAR models, validation results are generally expressed in terms of Q2 metrics. In this work, four fundamental mathematical principles, which should be respected by any Q2 metric, are introduced.

Molecular Dynamics

Influence of microhydration on the structures and proton-induced charge transfer in RNA intermediates

M. C. Bacchus-Montabonel [Université Claude Bernard Lyon 1], F. Calvo

J. Mol. Mod., **22**, 262, 2016.

Solvation effects are of major interest in the context of radiation damage, due to their potential applications in cancer therapy. Reliable modeling of the solvent is, however, quite challenging, and numerous studies have been devoted to isolated biomolecules and stepwise-hydrated molecules in which the amount of solvent is controlled one molecule at a time. The influence of stepwise hydration on radiation damage is investigated here using the example of proton-induced charge transfer in two biomolecular targets.

QM and QM/MM

Multiscale Quantum Mechanics/Molecular Mechanics Simulations with Neural Networks

Lin Shen, Jingheng Wu, and Weitao Yang [Duke University, Durham]

J. Chem. Theor. and Comp., **12**, 4934–4946, 2016.

Molecular dynamics simulation with multiscale quantum mechanics/molecular mechanics (QM/MM) methods is a very powerful tool for understanding the mechanism of chemical and biological processes in solution or enzymes. However, its computational cost can be too high for many biochemical systems because of the large number of ab initio QM calculations. Semiempirical QM/MM simulations have much higher efficiency. Its accuracy can be improved with a correction to reach the ab initio QM/MM level.

Improved Sugar Puckering Profiles for Nicotinamide Ribonucleoside for Hybrid QM/MM Simulations

Yaron Pshetitsky, Reuven Eitan, Gilit Verner, Amnon Kohen, and Dan Thomas Major [Bar-Ilan University]

J. Chem. Theor. and Comp., **12**, 5179–5189, 2016.

The coenzyme nicotinamide adenine dinucleotide (NAD⁺) and its reduced form (NADH) play ubiquitous roles as oxidizing and reducing agents in nature. The binding, and possibly the chemical redox step, of NAD⁺/NADH may be influenced by the cofactor conformational distribution and, in particular, by the ribose puckering of its nicotinamide–ribonucleoside (NR) moiety. In the present work we adopt an efficient and practical strategy to correct for this deficiency for NAD⁺/NADH.

Comparative Assessment of Different RNA Tetranucleotides from the DFT-D3 and Force Field Perspective

Rafał Szabla, Marek Havrila, Holger Kruse, and Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **120**, 10635–10648, 2016.

Classical force field (FF) molecular dynamics (MD) simulations of RNA tetranucleotides have substantial problems in reproducing conformer populations indicated by NMR experiments. To provide more information about the possible sources of errors, we performed quantum mechanical (QM, TPSS-D3/def2-TZVP) and molecular mechanics (MM, AMBER parm99bsc0+χOL3) calculations of different r(CCCC), r(GACC), and r(UUUU) conformers obtained from explicit solvent MD simulations. Solvent effects in the static QM and MM calculations were mimicked using implicit solvent models (COSMO and Poisson–Boltzmann, respectively).

Comparative or Homology Modeling

Homology modeling of a Class A GPCR in the inactive conformation: A quantitative analysis of the correlation between model/template sequence identity and model accuracy

Stefano Costanzi [American University, Washington], Matthew Skorski, Alessandro Deplano, Brett Habermehl, Mary Mendoza, Keyun Wang, Michelle Biederman, Jessica Dawson, Jia Gao

J. Mol. Graph. and Mod., **69**, 140–152, 2016.

With the present work we quantitatively studied the modellability of the inactive state of Class A G protein-coupled receptors (GPCRs). Specifically, we constructed models of one of the Class A GPCRs for which structures solved in the inactive state are available, namely the β2 AR, using as templates each of the other class members for which structures solved in the inactive state are also available. Our results showed a detectable linear correlation between model accuracy and model/template sequence identity.

Ligand Docking

Occupying a flat subpocket in a tRNA-modifying enzyme with ordered or disordered side chains: Favorable or unfavorable for binding?

Manuel Neeb, Christoph Hohn, Frederik Rainer Ehrmann, Adrian Härtsch, Andreas Heine, François Diederich, Gerhard Klebe [Philipps-Universität Marburg]

Bioorg. and Med. Chem., **24**, 4900-4910, 2016

Small-molecule ligands binding with partial disorder or enhanced residual mobility are usually assumed as unfavorable with respect to their binding properties. Considering thermodynamics, disorder or residual mobility is entropically favorable and contributes to the Gibbs energy of binding. In the present study, we analyzed a series of congeneric ligands inhibiting the tRNA-modifying enzyme TGT. Attached to the parent lin-benzoguanine scaffold, substituents in position 2 accommodate in a flat solvent-exposed pocket and exhibit varying degree of residual mobility.

Docking and DFT studies on ligand binding to Quercetin 2,3-dioxygenase

Aramice Y.S. Malkhasian & Brendan J. Howlin [University of Surrey, Guildford]

J. Biomol. Stru. And Dyn., **34**, 2453-2461, 2016.

Simple molecular docking calculations on quercetin, kojic acid and diethylcarbamatodithioic acid using the software package MOE are shown to be close to the geometries reported in the X-ray crystal structures of the protein co-crystallized with the respective ligands. Furthermore, DFT optimization of the docked conformations is shown to reproduce the essential features of previous studies on quercetin, showing that docking can be used to provide good starting structures for mechanistic study.

A mechanistic approach to explore novel HDAC1 inhibitor using pharmacophore modeling, 3D- QSAR analysis, molecular docking, density functional and molecular dynamics simulation study

Sanjay K. Choubey, Jeyakanthan Jeyaraman [Alagappa University, Karaikudi]

J. Mol.Graph. and Mod., **69**, 54-69, 2016.

Deregulated epigenetic activity of Histone deacetylase 1 (HDAC1) in tumor development and carcinogenesis pronounces it as promising therapeutic target for cancer treatment. HDAC1 has recently captured the attention of researchers owing to its decisive role in multiple types of cancer. In the present study a multistep framework combining ligand based 3D-QSAR, molecular docking and Molecular Dynamics (MD) simulation studies were performed to explore potential compound with good HDAC1 binding affinity.

Computational Modeling of β -Secretase 1 (BACE-1) Inhibitors Using Ligand Based Approaches

Govindan Subramanian [Worldwide Medicinal Chemistry], Bharath Ramsundar, Vijay Pande, and Rajiah Aldrin Denny

J.Chem. Infor. and Mod., **56**, 1936–1949, 2016.

The binding affinities (IC50) reported for diverse structural and chemical classes of human β -secretase 1 (BACE-1) inhibitors in literature were modeled using multiple in silico ligand based modeling approaches and statistical techniques. . The affinities were modeled using qualitative classification or quantitative regression schemes involving linear, nonlinear, and deep neural network (DNN) machine-learning methods used in the scientific literature for quantitative–structure activity relationships (QSAR).

Ligand Docking (Cont'd)

Sequence-Based Prediction of Protein–Carbohydrate Binding Sites Using Support Vector Machines

Ghazaleh Taherzadeh, Yaoqi Zhou, Alan Wee-Chung Liew, and Yuedong Yang [Griffith University, Parklands Drive]

J.Chem. Infor. and Mod., **56**, 2115–2122, 2016.

Carbohydrate-binding proteins play significant roles in many diseases including cancer. Here, we established a machine-learning-based method (called sequence-based prediction of residue-level interaction sites of carbohydrates, SPRINT-CBH) to predict carbohydrate-binding sites in proteins using support vector machines (SVMs). We found that integrating evolution-derived sequence profiles with additional information on sequence and predicted solvent accessible surface area leads to a reasonably accurate, robust, and predictive method.

Great interactions: How binding incorrect partners can teach us about protein recognition and function

Lydie Vamparys, Benoist Laurent, Alessandra Carbone and Sophie Sacquin-Mora [Institut de Biologie Physico-Chimique]

Proteins: Stru. Fun. & Bioinf., **84**, 1408–1421, 2016.

Protein–protein interactions play a key part in most biological processes and understanding their mechanism is a fundamental problem leading to numerous practical applications. The prediction of protein binding sites in particular is of paramount importance since proteins now represent a major class of therapeutic targets. From the analysis of the protein interfaces generated by a massive cross-docking experiment using the 168 proteins of the Docking Benchmark 2.0, where all possible protein pairs, and not only experimental ones, have been docked together, we show that it is also possible to predict a protein's binding residues without having any prior knowledge regarding its potential interaction partners.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 70, November, 2016.

- 1-6 **Volume-rendering on a 3D hyperwall: A molecular visualization platform for research, education and outreach**, Preston J. MacDougall, Christopher E. Henze, Anatoliy Volkov [Middle Tennessee State University]

See Applications / Bioinformatics.

- 7-13 **H-bond and dipole–dipole interactions between water and COO functional group in methyl benzoate derivatives: Substituent and heteroatom effects**, S. Sarhadinia, A. Ebrahimi [University of Sistan and Baluchestan]

Interactions of COOCH₃ functional group of methyl benzoate (MB) and its derivatives can substantially be affected by substituents and heteroatoms. The substituent and heteroatom effects on the intermolecular interactions in the complexes of MB and its derivatives with the water molecule have been investigated by the quantum mechanical calculations in the present study.

- 14-22 **Integration of ligand and structure based approaches for identification of novel MbtI inhibitors in Mycobacterium tuberculosis and molecular dynamics simulation studies**, Lakshmi Maganti, Pradeep Grandhi, Nanda Ghoshal [CSIR-Indian Institute of Chemical Biology]

See Applications / Ligand Binding.

- 23-29 **A DFT-based QSAR study on inhibition of human dihydrofolate reductase**, Sedat Karabulut [Balikesir University, Balikesir], Natalia Sizochenko, Adnan Orhan, Jerzy Leszczynski

See Methodology / QSAR.

- 30-39 **Structural and dynamic insights into the C-terminal extension of cysteine proteinase B from Leishmania amazonensis**, Deborah Antunes Santos, Mauricio Garcia de Souza Costa, Carlos Roberto Alves, Ernesto Raul Caffarena [Programa De Computação Científica]

See Applications / Homology Modeling.

- 40-44 **Molecular design and validation of halogen bonding orthogonal to hydrogen bonding in breast cancer MDM2–peptide complex**, Anzhong Huang, Liang Zhou [Jinshan Hospital, Fudan University], Dawei Zhang, Junliang Yao, Yong Zhang

See Applications / Ligand Binding.

- 45-53 **Double hydrogen bond interaction in 7-azaindole complexes with protic solvents**, Sara Fakhraee [Payame Noor University], Maryam Souri

The double hydrogen bond interaction between 7-azaindole (7AI) and protic solvents including methanol (MeOH), formamide (FM), formic acid (FA), pyridone (PY) and 7AI has been investigated as a proper model of mutations generated by tautomeric shifts in hydrogen-bonded bases of DNA.

- 54-69 **A mechanistic approach to explore novel HDAC1 inhibitor using pharmacophore modeling, 3D- QSAR analysis, molecular docking, density functional and molecular dynamics simulation study**, Sanjay K. Choubey, Jeyakanthan Jeyaraman [Alagappa University, Karaikudi]

See Methodology / Ligand Docking.

- 70-76 **pH-controlled doxorubicin anticancer loading and release from carbon nanotube noncovalently modified by chitosan: MD simulations**, Chompoonut Rungnim, Thanyada Rungrotmongkol, Rungtiva P. Poo-arporn [King Mongkut's University of Technology Thonburi]

See Applications / Protein Dynamics.

- 77-84 **The effect of protonation of cytosine and adenine on their interactions with carbon nanotubes**, Marina V. Kosevich [University of Arizona, Tucson], Valentina G. Zobnina, Stepan G. Stepanian, Victor A. Karachevtsev, Ludwik Adamowicz

See Applications / Carbon Nanotubes.

- 85-93 **Identification of non-resistant ROS-1 inhibitors using structure based pharmacophore analysis**, Disha Pathak, Navriti Chadha, Om Silakari [Punjabi University, Patiala]

See Applications / Medicinal Chemistry and Drug Design.

- 94-99 **Molecular simulation study on concentration effects of rofecoxib with POPC bilayer**, Huanjie Wang, Fancui Meng [Tianjin Institute of Pharmaceutical Research]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

- 100-108 **Molecular simulations of lactose-bound and unbound forms of the FaeG adhesin reveal critical amino acids involved in sugar binding**, Joseph L. Baker [The College of New Jersey], Heba Jafri

See Applications / Ligand Binding.

- 109-121 **Molecular simulation study of the unbinding of α -conotoxin [Y4E]GID at the $\alpha 7$ and $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors**, Abishek Suresh, Andrew Hung [School of Science, RMIT University]

See Applications / Ligand Binding.

- 122-128 **Multi scale modeling of 2450 MHz electric field effects on microtubule mechanical properties**, S.S. Setayandeh, A. Lohrasebi [University of Isfahan]

See Applications / Protein Dynamics.

- 129-139 **In silico approaches and proportional odds model towards identifying selective ADAM17 inhibitors from anti-inflammatory natural molecules**, Pallab Kumar Borah, Sourav Chakraborty, Anupam N. Jha, Sanchaita Rajkhowa, Raj Kumar Duary [Tezpur University, Napaam]

See Applications / Medicinal Chemistry and Drug Design.

- 140-152 **Homology modeling of a Class A GPCR in the inactive conformation: A quantitative analysis of the correlation between model/template sequence identity and model accuracy**, Stefano Costanzi [American University, Washington], Matthew Skorski, Alessandro Deplano, Brett Habermehl, Mary Mendoza, Keyun Wang, Michelle Biederman, Jessica Dawson, Jia Gao

See Methodology / Homology Modeling.

- 153-162 **Effect of allosteric molecules on structure and drug affinity of HIV-1 protease by molecular dynamics simulations**, Xian-Mei Meng, Wei-Jun Hu, Yu-Guang Mu [Nanyang Technological University], Xie-Huang Sheng

See Applications / Ligand Binding.

- 163-169 **DFT simulation towards evaluation the molecular structure and properties of the heterogeneous C16Mg8O8 nano-cage as selective nano-sensor for H2 and N2 gases**, Parnia Abyar Ghamsari, Milad Nouraliei [Islamic Azad University], Sara Soleimani Gorgani

Adsorption of hydrogen (H₂) and nitrogen (N₂) molecules was analyzed on a new fullerene-like C₁₆Mg₈O₈ nano-cage, composed of magnesium, oxygen, and carbon, using density functional theory. A detailed analysis of the energy, geometry, and electronic structure of various H₂ and N₂ adsorptions on the cluster surface was performed.

- 170-180 **A comparative study based on docking and molecular dynamics simulations over HDAC-tubulin dual inhibitors**, Malihe Hassanzadeh, Kowsar Bagherzadeh, Massoud Amanlou [Tehran University of Medical Sciences]

See Applications / Medicinal Chemistry and Drug Design.

- 181-195 **A molecular dynamics study of the BACE1 conformational change from Apo to closed form induced by hydroxyethylamine derived compounds**, Carlos Gueto-Tettay, Joshua Zuchniarz, Yeyson Fortich-Seca, Luis Roberto Gueto-Tettay, Juan Carlos Drosos-Ramirez [Universidad de Cartagena]

See Applications / Protein Conformational Analysis.

- 196-211 **Computational design of graphene sheets for withstanding the impact of ultrafast projectiles**, Sadegh Sadeghzadeh [Iran University of Science and Technology]

A multi-scale method is employed in this paper to conduct a virtual study of the high-strain behavior of single- and multi-layer graphene sheets and to investigate the design of related graphene-based devices.

Journal of Computational Chemistry, 37 (29), November, 2016.

- 2553–2563 **Monte Carlo simulation algorithm for B-DNA**, Steven C. Howell, Xiangyun Qiu and Joseph E. Curtis [NIST Center for Neutron Research]

See Applications / Nucleic Acids.

- 2564–2572 **Parameterization of the ReaxFF reactive force field for a proline-catalyzed aldol reaction**, Pierre O. Hubin [University of Namur], Denis Jacquemin, Laurence Leherite and Daniel P. Vercauteren

A parameterization of the ReaxFF reactive FF is performed using a Monte Carlo Simulated Annealing procedure for the modeling of a proline-catalyzed aldol reaction. Emphasis is put on the accurate reproduction of the relative stabilities of several key intermediates of the reaction, as well as, on the description of the reaction path bridging these intermediates based on quantum mechanical calculations.

- 2573–2587 **A pH-dependent computational approach to the effect of mutations on protein stability**, Velin Z. Spassov [BIOVIA, Dassault Systemes] and Lisa Yan

See Applications / Protein Dynamics.

- 2588–2596 **A QTAIM and stress tensor investigation of the torsion path of a light-driven fluorene molecular rotary motor**, Ming Xing Hu, Tianlv Xu, Roya Momen, Guo Huan, Steven R. Kirk, Samantha Jenkins and Michael Filatov [Ulsan National Institute of Science and Technology]

The utility of the QTAIM/stress tensor analysis method for characterizing the photoisomerization of light driven molecular rotary machines is investigated on the example of the torsion path in fluorene molecular motor.

- 2597–2605 **Free-energy calculations of residue mutations in a tripeptide using various methods to overcome inefficient sampling**, Michael M. H. Graf, Manuela Maurer and Chris Oostenbrink [University of Natural Resources and Life Sciences, Vienna]

Previous free-energy calculations have shown that the seemingly simple transformation of the tripeptide KXX to KGK in water holds some unobvious challenges concerning the convergence of the forward and backward thermodynamic integration processes (i.e., hysteresis). In the current study, the central residue X was either alanine, serine, glutamic acid, lysine, phenylalanine, or tyrosine.

Journal of Computational Chemistry, 37 (30), November, 2016.

- 2623–2633 **Massively parallel algorithm and implementation of RI-MP2 energy calculation for peta-scale many-core supercomputers**, Michio Katouda, Akira Naruse, Yukihiro Hirano and Takahito Nakajima [RIKEN Advanced Institute for Computational Science]

A new parallel algorithm and its implementation for the RI-MP2 energy calculation utilizing peta-flop-class many-core supercomputers are presented.

- 2634–2646 **A kinetic chain growth algorithm in coarse-grained simulations**, Hong Liu [Jilin University, Changchun], You-Liang Zhu, Zhong-Yuan Lu and Florian Müller-Plathe

We propose a kinetic chain growth algorithm for coarse-grained (CG) simulations in this work. By defining the reaction probability, it delivers a description of consecutive polymerization process. This algorithm is validated by modeling the process of individual styrene monomers polymerizing into polystyrene chains, which is proved to correctly reproduce the properties of polymers in experiments.

- 2647–2658 **Assessing the attractive/repulsive force balance in axial cyclohexane C–Hax···Yax contacts: A combined computational analysis in monosubstituted cyclohexanes**, Carlos Silva Lopez, Olalla Nieto Faza, Frank De Proft and Antonios Kolocouris [National and Kapodistrian University of Athens]

The interactions of axial substituents in monosubstituted cyclohexane rings are studied in this work using an array of different computational techniques. Additionally, the anomalous axial preference for some bulky substituents is related to stabilizing dispersion interactions.

- 2659–2666 **The role of dispersive forces determining the energetics of adsorption in Ti zeolites**, Matteo Signorile, Alessandro Damin [Università di Torino, Torino], Francesca Bonino, Valentina Crocellà, Carlo Lamberti and Silvia Bordiga

Ti-zeolites are interesting materials because of their key role in partial oxidation reactions, as well as under a fundamental point of view being regarded as single site catalysts. . The present work wants to underline the role of dispersive forces in correctly determining the adsorption energies of H₂O and NH₃ in Ti chabazite.

Journal of Molecular Modeling, 22 (11), November, 2016.

- 255 **Insights into the spontaneity of hydrogen bond formation between formic acid and phthalimide derivatives**, Rogério V. A. Júnior, Gustavo L. C. Moura, Nathalia B. D. Lima [Universidade Federal de Pernambuco]

We evaluated a group of phthalimide derivatives, which comprise a convenient test set for the study of the multiple factors involved in the energetics of hydrogen bond formation. Accordingly, we carried out quantum chemical calculations on the hydrogen bonded complexes formed between a sample of phthalimide derivatives with formic acid with the intent of identifying the most important electronic and structural factors related to how their strength and spontaneity vary across the series.

- 256 **3D structure prediction of histone acetyltransferase proteins of the MYST family and their interactome in *Arabidopsis thaliana***, A. V. Raevsky [National Academy of Sciences of Ukraine], M. Sharifi, D. A. Samofalova, P. A. Karpov, Y. B. Blume

See Applications / Protein Structure Analysis.

- 257 **Theoretical studies on the hydrogen-bonding interactions between luteolin and water: a DFT approach**, Yan-Zhen Zheng, Yu Zhou, Qin Liang, Da-Fu Chen [Fujian Agriculture and Forestry University], Rui Guo

Flavonoids are among the most important bioactive compounds responsible for the medical properties of honey and propolis. Water is the solvent most commonly used to extract flavonoids from honey and propolis. In this work, hydrogen-bonding interactions between a representative flavonoid, luteolin, and water were investigated by density functional theory (DFT) from a theoretical viewpoint.

- 258 **Protein remains stable at unusually high temperatures when solvated in aqueous mixtures of amino acid based ionic liquids**, Guillaume Chevrot, Eudes Eterno Fileti [Universidade Federal de São Paulo], Vitaly V. Chaban

See Applications / Protein Dynamics.

- 259 **A method for predicting individual residue contributions to enzyme specificity and binding-site energies, and its application to MTH1**, James J. P. Stewart [Stewart Computational Chemistry]

See Applications / Enzyme Catalysis.

- 260 **Calculations of BODIPY dyes in the ground and excited states using the M06-2X and PBE0 functionals**, Marina Laine, Nuno A. Barbosa, Robert Wieczorek, Mikhail Ya. Melnikov, Aleksander Filarowski [University of Wroclaw]

A number of fluorescent dyes based on BODIPY (4,4'-difluoro-4-bora-3a,4a-diaza-s-indacene) have been studied theoretically. This paper presents the results of calculations of these BODIPY dyes in their ground and excited states, performed using DFT and TD-DFT methods, respectively.

- 261 **A theoretical analysis of substituent electronic effects on phosphine-borane bonds**, Paul A. Sibbald [Stetson University]

Phosphine-borane adducts are a well-known moiety in synthetic and coordination chemistry. These complexes form a dative bond in which the Lewis basic phosphorus atom donates electron density into an empty p-orbital of the Lewis acidic boron atom. This paper describes a detailed density functional theory level (B3LYP) study completed to determine the impact electron-donating and withdrawing substituents have on phosphine-borane bonds through the investigation of a series of para-substituted $\text{PAr}_3\text{-BH}_3$ and $\text{PH}_3\text{-BAr}_3$ phosphine-borane adducts.

- 262 **Influence of microhydration on the structures and proton-induced charge transfer in RNA intermediates**, M. C. Bacchus-Montabonel [Université Claude Bernard Lyon 1], F. Calvo

See Methodology / Molecular Dynamics.

- 263 **Formazanate boron difluoride dyes: discrepancies between TD-DFT and wavefunction descriptions**, Adèle D. Laurent, Edwin Otten, Boris Le Guennic, Denis Jacquemin [Université de Nantes]

In this work, we investigate the ground- and excited-state structures as well as the optical properties of a series of five formazanate dyes using state-of-the-art density-based and wavefunction-based methods. The present work is the first to evaluate the properties of formazanate-BF₂ dyes with wavefunction-correlated schemes.

- 264 **In silico study of amphiphilic nanotubes based on cyclic peptides in polar and non-polar solvent**, Vinodhkumar Vijayakumar, Ramadoss Vijayaraj, Günther H. Peters [Technical University of Denmark]

See Applications / Protein Dynamics.

- 265 **Vibronic coupling to simulate the phosphorescence spectra of Ir(III)-based OLED systems: TD-DFT results meet experimental data**, Houmam Belaidi, Salah Belaidi, Claudine Katan, Camille Latouche, Abdou Boucekkine [Université de Nantes]

The electronic and optical properties of six iridium imidazolylidene complexes (1a, 1b, 2, 2b, 3, 3b) that are strong candidates for use in OLED systems were investigated theoretically. Computations using DFT and TD-DFT methods were performed to explain the observed optical properties of these complexes.

- 266 **Altered torquoselectivity of fluorine in the iron-tricarbonyl-mediated thermal ring opening of 3-fluorocyclobutene: a density-functional exploration**, Chandresakaran Prathipa, Lakshminarayanan Akilandeswari [Sri Sarada College for Women, Salem]

There are eight possible pathways for the iron-tricarbonyl-assisted thermal electrocyclic ring opening of fluorocyclobutene due to variations in the orientation of the binding of Fe(CO)₃ relative to the fluorine substituent (R1 or R2), stereoselectivity (conrotatory or disrotatory, i.e., C or D), and the torquoselectivity of fluorine (inward-facing or outward-facing, i.e., in or out). A density functional study revealed that the energetically favored pathway is R1Din.

Molecular Simulation, 42 (17), September, 2016.

- 1429-1436 **Adsorption behaviors of hydrogen sulphide on Au(110) nanoslit array surfaces using molecular dynamics simulations**, Jenn-Kun Kuo, Pei-Hsing Huang [National Pingtung University of Science and Technology], Tzu-Hsiu Huang & Jheng-Yu Luo

The adsorption behaviour of gas molecules on detector surfaces has a profound influence on the sensitivity of the detector. For this reason, this study used molecular dynamics simulation to explore the dynamic adsorption behaviour of hydrogen sulphide (H₂S) molecules on various types of Au surfaces, including a planar Au(1 1 0) structure and three types of slit array structures.

- 1437-1443 **Soft ellipsoid potential for biaxial molecules**, Jayashree Saha [University of Calcutta]

A soft ellipsoid contact pair potential model for biaxial molecules is proposed considering the configuration dependent energy anisotropy explicitly alongwith their geometrical aspects.

- 1444-1451 **Molecular dynamics simulation to investigate anhydrous phosphoric acid-doped polybenzimidazole**, Chung-Te Chang Chien, Po-Hsiang Chuang & Cheng-Lung Chen [Sun Yat-Sen University]

The study conducted a molecular dynamics simulation based on a condensed-phase optimised molecular potentials for atomistic simulation studies force field model to investigate an anhydrous system of phosphoric acid-doped polybenzimidazole (poly[2,2'-(m-phenylene)-5,5'-bibenzimidazole], PBI).

- 1452-1459 **Droplets motion on chemically/topographically heterogeneous surfaces**, Jiayi Zhao, Shuo Chen [Tongji University, Shanghai] & Yang Liu

We present a numerical study of droplets sliding across chemically heterogeneous surfaces formed by a periodic pattern of alternating hydrophobic and hydrophilic stripes, or topographically heterogeneous surfaces which are microgrooved.

- 1460-1467 **The binding affinity of human serum albumin and paclitaxel through MMPBSA based on docked complex**, Huaxing Yu, Daixi Li [University of Shanghai for Science and Technology], Fei Xu, Qi Pan, Pei Chai, Baolin Liu & Chenglung Chen

See Applications / Ligand Binding.

- 1468-1474 **Chrysophanol anthrone: a theoretical study on the potential energy surface**, Fernando J. Tun-Rosado, Gonzalo J. Mena-Rejón, Rubén M. Carballo, Gumersindo Mirón-López & Ramiro F. Quijano-Quñones [Universidad Autonoma de Yucatan]

The potential energy surface (PES) of chrysophanol anthrone, the active component of Goa Powder, was systematically explored and thoroughly scrutinised via density functional theory, in order to gain an understanding of its physicochemical properties.

- 1475-1484 **A molecular dynamics simulation study of the effect of water-graphene interaction on the properties of confined water**, Farkhondeh Mozaffari [Persian Gulf University, Bushehr]

The role of water in determining the structure and stability of biomacromolecules has been well studied. In this work, molecular dynamics simulations have been applied to investigate the effect of surface hydrophobicity on the structure and dynamics of water confined between graphene surfaces.

- 1485-1489 **Effect of hydrogen coverage on the buckling of penta-graphene by molecular dynamics simulation**, Sadollah Ebrahimi [University of Kurdistan, Sanadaj]

By employing a series of MD simulations, buckling behaviour of penta-graphene and functionalised penta-graphene having different hydrogen (H) coverage is presented in this study. To this end, the buckling onset strain is determined for different systems. The results reveal that the new allotrope is slightly stiffer than graphene.

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