



Results

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Structural modeling and docking studies of ribose 5-phosphate isomerase from *Leishmania major* and *Homo sapiens*: A comparative analysis for Leishmaniasis treatment

Priscila V.S.Z. Capriles [Laboratório Nacional de Computação Científica], Luiz Phillippe R. Baptista, Isabella A. Guedes, Ana Carolina R. Guimarães, Fabio L. Custódio, Marcelo Alves-Ferreira, Laurent E. Dardenne

J. Mol.Graph. and Mod., 55,134-147,2015.

Leishmaniasis are caused by protozoa of the genus *Leishmania* and are considered the second-highest cause of death worldwide by parasitic infection. The drugs available for treatment in humans are becoming ineffective mainly due to parasite resistance; therefore, it is extremely important to develop a new chemotherapy against these parasites. In this work, through an in silico comparative analysis between the genomes of *Leishmania major* and *Homo sapiens*, the enzyme ribose 5-phosphate isomerase (R5PI) was indicated as a promising molecular target. R5PI is an important enzyme that acts in the pentose phosphate pathway and catalyzes the interconversion of D-ribose-5-phosphate (R5P) and D-ribulose-5-phosphate (5RP).

Synthesis, biological evaluation and 3D-QSAR study of novel 4,5-dihydro-1H-pyrazole thiazole derivatives as BRAF^{V600E} inhibitors

Meng-Yue Zhao, Yong Yin, Xiao-Wei Yu, Chetan B. Sangani, Shu-Fu Wang, Ai-Min Lu, Li-Fang Yang, Peng-Cheng Lv, Ming-Guo Jiang, Hai-Liang Zhu[Nanjing University]

Bioorg. and Med.Chem., 23, 46-54 ,2015.

Many reports implied that the BRAF serine/threonine kinase was mutated in various types of human tumors, which were related with cell growth, survival and differentiation. To provide new therapeutic opportunities, a series of novel 4,5-dihydro-1H-pyrazole derivatives (**6a–10d**) containing thiazole moiety as potential V600E mutant BRAF kinase (BRAF^{V600E}) inhibitors were designed and synthesized. All compounds were evaluated in vitro for anticancer activities against WM266.4 human melanoma cell line and breast cancer MCF-7 cell line. Compound **10d** displayed the most potential antiproliferative activity with an IC₅₀ value of 0.12 µM against cell line WM266.4 and 0.16 µM against MCF-7 with positive control Sorafenib.

 MMCC Results 8013 Los Sabalos Street San Diego, CA 92126 Tel. (858) 663-0162 e-mail: mmccresults@gmail.com Dr. R. Mutyala, RR Labs Inc., 8013 Los Sabalos St. San Diego, CA 92126 Editors Emeritus: Bruce Gelin, Ph.D. David Busath, M.D. <i>Dr. Gelin was founder of MMCC Results and edited volumes 1-6. Dr. David Busath edited volumes 7-14</i>	MMCC Results (ISSN 1061-6381) is published ten times per year at the beginning of each month except January and August by the independent business, MMCC Results. Mention of software, hardware, or other products is for informational purposes only and does not constitute an endorsement or recommendation by MMCC Results nor by the authors of the paper cited. All product names are the trademarks or registered symbols of their respective holders. Marginal symbols indicate that the authors acknowledged the use of a software package from a commercial source. A refers to Accelrys Inc. and T to Tripos Inc. Other companies are denoted by their name in a box. Papers of special interest are marked by an exclamation point [!]. Copyright © 2006 MMCC Results	Assistant Editors: Sowmya .N Rational Labs, Hyderabad., India Sambasivareddy M RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

Computational Design and Discovery of Nanomolar Inhibitors of I κ B Kinase β

Hwangseo Park, Yongje Shin, Hyeonjeong Choe, Sungwoo Hong [Korea Advanced Institute of Science and Technology (KAIST)]

J. Am. Chem. Soc., **137**, 337–348, 2015.

I κ B kinase β (IKK β) is a useful target for the discovery of new medicines for cancer and inflammatory diseases. We aimed to identify new classes of potent IKK β inhibitors based on structure-based virtual screening, de novo design, and chemical synthesis. To increase the probability of finding actual inhibitors, we improved the scoring function for the estimation of the IKK β -inhibitor binding affinity by introducing proper solvation free energy and conformational destabilization energy terms for putative inhibitors. Using this modified scoring function, we were able to identify 15 submicromolar-level IKK β inhibitors that possess the phenyl-(4-phenyl-pyrimidin-2-yl)-amine moiety as the molecular core.

Formation of 3D Cholesterol Crystals from 2D Nucleation Sites in Lipid Bilayer Membranes: Implications for Atherosclerosis

Neta Varsano, Iael Fargion, Sharon G. Wolf, Leslie Leiserowitz, Lia Addadi [Weizmann Institute of Science]

J. Am. Chem. Soc., **137**, 1601–1607, 2015.

Atherosclerosis is the major precursor of cardiovascular disease. The formation of cholesterol crystals in atherosclerotic plaques is associated with the onset of acute pathology. The cholesterol crystals induce physical injury in the plaque core, promoting cell apoptosis and triggering an increased inflammatory response. Herein we address the question of how cholesterol crystal formation occurs in atherosclerosis. We demonstrate that three-dimensional (3D) cholesterol crystals can undergo directed nucleation from bilayer membranes containing two-dimensional (2D) cholesterol crystalline domains.

Quantum-chemistry based calibration of the alkali metal cation series (Li⁺—Cs⁺) for large-scale polarizable molecular mechanics/dynamics simulations

Todor Dudev, Mike Devereux, Markus Meuwly, Carmay Lim, Jean-Philip Piquemal, Nohad Gresh [Université Paris Descartes]

J. Comp. Chem., **36**, 285–302, 2015.

The alkali metal cations in the series Li⁺—Cs⁺ act as major partners in a diversity of biological processes and in bioinorganic chemistry. In this article, we present the results of their calibration in the context of the SIBFA polarizable molecular mechanics/dynamics procedure. It relies on quantum-chemistry (QC) energy-decomposition analyses of their monoligated complexes with representative O—, N—, S—, and Se— ligands, performed with the aug-cc-pVTZ(-f) basis set at the Hartree–Fock level. Close agreement with QC is obtained for each individual contribution, even though the calibration involves only a limited set of cation-specific parameters.

Function-Oriented Development of CXCR4 Antagonists as Selective Human Immunodeficiency Virus (HIV)-1 Entry Inhibitors

Chien-Huang Wu, Chuan-Jen Wang, Chun-Ping Chang, Yung-Chi Cheng, Jen-Shin Song, Jiing-Jyh Jan, Ming-Chen Chou, Yi-Yu Ke, Jing Ma, Ying-Chieh Wong, Tsung-Chih Hsieh, Yun-Chen Tien, Elizabeth A. Gullen, Chen-Fu Lo, Chia-Yi Cheng, Yu-Wei Liu, Amit A. Sadani, Chia-Hua Tsai, Hsin-Pang Hsieh, Lun K. Tsou, Kak-Shan Shia [National Health Research Institutes, Miaoli County]

J. Med. Chem., **58**, 1452–1465, 2015.

Motivated by the pivotal role of CXCR4 as an HIV entry co-receptor, we herein report a de novo hit-to-lead effort on the identification of subnanomolar purine-based CXCR4 antagonists against HIV-1 infection. Compound 24, with an EC₅₀ of 0.5 nM against HIV-1 entry into host cells and an IC₅₀ of 16.4 nM for inhibition of radioligand stromal-derived factor-1 α (SDF-1 α) binding to CXCR4, was also found to be highly selective against closely related chemokine receptors. We rationalized that compound 24 complementarily interacted with the critical CXCR4 residues that are essential for binding to HIV-1 gp120 V3 loop and subsequent viral entry.

Medicinal Chemistry and Drug Design (Cont'd)

Discovery of Small Molecule Inhibitors to Krüppel-like Factor 10 (KLF10): Implications for Modulation of T Regulatory Cell Differentiation

Santosh A. Khedkar, Xinghui Sun, Alan C. Rigby, Mark W. Feinberg[Harvard Medical School]

J.Med.Chem., **58**, 1466–1478, 2015.

The Krüppel-like family of transcription factors (KLFs) constitute a subfamily of C2H2-type zinc finger proteins with distinct cell-type expression patterns and regulate functional aspects of cell growth and differentiation, activation, or development. To date, there are no selective pharmacological inhibitors to KLF10. Herein, we report on the discovery of first-in-class small molecule compounds that inhibit the KLF10-DNA interaction interface using computer-aided drug design (CADD) screens of chemical libraries. Interrogation of a “druggable” pocket in the second zinc finger of KLF10 revealed three small molecules, #48, #48-15, and #15-09, with similar scaffolds and binding patterns.

Exploration of the structural requirements of HIV-protease inhibitors using pharmacophore, virtual screening and molecular docking approaches for lead identification

Md Ataul Islam, Tahir S. Pillay[University of Pretoria and National Health Laboratory Service]

J. Mol.Graph. and Mod., **56**, 20-30,2015.

Pharmacoinformatics approaches are widely used in the field of drug discovery as it saves time, investment and animal sacrifice. In the present study, pharmacore-based virtual screening was adopted to identify potential HIV-protease ligands as anti-HIV agents. Pharmacophore is the 3D orientation and spatial arrangement of functional groups that are critical for binding at the active site cavity. Virtual screening retrieves potential hit molecules from databases based on imposed criteria. A set of 30 compounds were selected with inhibition constant as training set from 129 compounds of dataset set and subsequently the pharmacophore model was developed.

Exploring the drug resistance of V32I and M46L mutant HIV-1 protease to inhibitor TMC114: Flap dynamics and binding mechanism

Biswa Ranjan Meher, Yixuan Wang[Albany State University]]

J. Mol.Graph. and Mod., **56**, 60-73, 2015.

Inhibitors of HIV-1 protease (HIV-1-pr) generally only bind to the active site of the protease. However, for some mutants such as V32I and M46L the TMC114 can bind not only to the active cavity but also to the groove of the flexible flaps. Although the second binding site suggests the higher efficiency of the drug against HIV-1-pr, the drug resistance in HIV-1-pr due to mutations cannot be ignored, which prompts us to investigate the molecular mechanisms of drug resistance and behavior of double bound TMC114 (2T) to HIV-1-pr. The conformational dynamics of HIV-1-pr and the binding of TMC114 to the WT, V32I and M46L mutants were investigated with all-atom molecular dynamic (MD) simulation.

Medicinal Chemistry and Drug Design (Cont'd)

Targeting a cluster of arginine residues of neuraminidase to avoid oseltamivir resistance in influenza A (H1N1): a theoretical study

L. Ramírez-Salinas, Gema, L. E. Tolentino-Lopez, F. Martínez-Ramos, I. Padilla-Martínez, J. García-Machorro, J. Correa-Basurto [Instituto Politécnico Nacional]

J. Mol.Mod., **21**, 8, 2015.

Following the influenza A (H1N1) pandemic in Mexico and around the world in 2009, the numbers of oseltamivir-resistant clinical cases have increased through a mechanism that remains unclear. In this work, we focus on studying the mutated NA structures ADA71175 (GenBank) and 3CKZ (PDB ID). Recently crystallized NA (PDB ID: 3NSS) was used as a wild-type structure and template to construct the three-dimensional (3D) structure of ADA71175. Then, the NA mutants and 3NSS natives as well as their refined monomer structures as determined through MD simulations (snapshots at 50 ns) were used as models to perform a docking study using a set of aryl-oseltamivir derivatives.

Atomistic insights into the lung cancer-associated L755P mutation in HER2 resistance to lapatinib: a molecular dynamics study

Bei Yang, Haiping Zhang, Hao Wang [Tongji University]

J. Mol.Mod., **21**, 24, 2015.

HER2, a member of the human ErbB protein family belonging to receptor tyrosine kinases, plays important roles in regulating crucial cellular processes, including cell migration, proliferation, and differentiation. A missense mutation, L755P, in the HER2 kinase domain has been involved in lung cancer in humans and exhibits reduced response to lapatinib therapy. However, the detailed mechanism of how the HER2 L755P mutation causes drug resistance to lapatinib remains elusive. Here, molecular docking, molecular dynamics (MD) simulations, binding free energy calculations [molecular mechanics and generalized Born/surface area (MM-GBSA)] were performed to reveal the mechanism of drug resistance due to the HER2 L755P mutation.

Identification of a novel carbohydrate esterase from *Bjerkandera adusta*: Structural and function predictions through bioinformatics analysis and molecular modeling

Laura I. Cuervo-Soto, Gilberto Valdés-García, Ramón Batista-García, María del Rayo Sánchez-Carbente, Edgar Balcázar-López, Verónica Lira-Ruan, Nina Pastor, Jorge Luis Folch-Mallol [Universidad Autónoma del Estado de Morelos. Av]

Proteins: Stru. Fun. & Bioinf., **83**, 533–546, 2015.

A new gene from *Bjerkandera adusta* strain UAMH 8258 encoding a carbohydrate esterase (designated as BacesI) was isolated and expressed in *Pichia pastoris*. The gene had an open reading frame of 1410 bp encoding a polypeptide of 470 amino acid residues, the first 18 serving as a secretion signal peptide. Homology and phylogenetic analyses showed that BaCesI belongs to carbohydrate esterases family 4. Three-dimensional modeling of the protein and normal mode analysis revealed a breathing mode of the active site that could be relevant for esterase activity. Furthermore, the overall negative electrostatic potential of this enzyme suggests that it degrades neutral substrates and will not act on negative substrates such as peptidoglycan or p-nitrophenol derivatives.

Medicinal Chemistry and Drug Design (Cont'd)

Study of Chromatographic Retention of Natural Terpenoids by Chemoinformatic Tools

Tiago B. Oliveira, Leonardo Gobbo-Neto, Thomas J. Schmidt, Fernando B. Da Costa [University of São Paulo (USP)]

J.Chem. Infor. and Mod. **55**, 26–38, 2015.

The study of chromatographic retention of natural products can be used to increase their identification speed in complex biological matrices. In this work, six variables were used to study the retention behavior in reversed phase liquid chromatography of 39 sesquiterpene lactones (SL) from an in-house database using chemoinformatics tools. To evaluate the retention of the SL, retention parameters on an ODS C-18 column in two different solvent systems were experimentally obtained, namely, MeOH–H₂O 55:45 and MeCN–H₂O 35:75.

In silico screening for *Plasmodium falciparum* enoyl-ACP reductase inhibitors

Steffen Lindert [University of California San Diego], Lorillee Tallorin, Quynh G. Nguyen, Michael D. Burkart, J. Andrew McCammon

J.Comp.Aided. Mol.des. **29**, 79-87, 2015.

The need for novel therapeutics against *Plasmodium falciparum* is urgent due to recent emergence of multi-drug resistant malaria parasites. Since fatty acids are essential for both the liver and blood stages of the malarial parasite, targeting fatty acid biosynthesis is a promising strategy for combatting *P. falciparum*. We present a combined computational and experimental study to identify novel inhibitors of enoyl-acyl carrier protein reductase (*Pf*ENR) in the fatty acid biosynthesis pathway. A small-molecule database from ChemBridge was docked into three distinct *Pf*ENR crystal structures that provide multiple receptor conformations.

Identification of ligand efficient, fragment-like hits from an HTS library: structure-based virtual screening and docking investigations of 2*H*- and 3*H*-pyrazolo tautomers for Aurora kinase A selectivity

Sailu Sarvagalla, Vivek Kumar Singh, Yi-Yu Ke, Hui-Yi Shiao, Wen-Hsing Lin, Hsing-Pang Hsieh, John T. A. Hsu, Mohane Selvaraj Coumar [Pondicherry University]

J.Comp.Aided. Mol.des. **29**, 89-100, 2015.

Furanopyrimidine **1** (IC₅₀ = 273 nM, LE = 0.36, LELP = 10.28) was recently identified by high-throughput screening (HTS) of an in-house library (125,000 compounds) as an Aurora kinase inhibitor. Structure-based hit optimization resulted in lead molecules with in vivo efficacy in a mouse tumour xenograft model, but no oral bioavailability. This is attributed to “molecular obesity”, a common problem during hit to lead evolution during which degradation of important molecular properties such as molecular weight (MW) and lipophilicity occurs. This could be effectively tackled by the right choice of hit compounds for optimization. In this regard, ligand efficiency (LE) and ligand efficiency dependent lipophilicity (LELP) indices are more often used to choose fragment-like hits for optimization.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of antipsychotic drug fluspirilene as a potential p53-MDM2 inhibitor: a combined computational and experimental study

Sachin P. Patil [Widener University], Michael F. Pacitti, Kevin S. Gilroy, John C. Ruggiero, Jonathan D. Griffin, Joseph J. Butera, Joseph M. Notarfrancesco, Shawn Tran, John W. Stoddart

J.Comp.Aided. Mol.des. **29**, 155-163, 2015.

The inhibition of tumor suppressor p53 protein due to its direct interaction with oncogenic murine double minute 2 (MDM2) protein, plays a central role in almost 50 % of all human tumor cells. Therefore, pharmacological inhibition of the p53-binding pocket on MDM2, leading to p53 activation, presents an important therapeutic target against these cancers expressing wild-type p53. In this context, the present study utilized an integrated virtual and experimental screening approach to screen a database of approved drugs for potential p53-MDM2 interaction inhibitors. Specifically, using an ensemble rigid-receptor docking approach with four MDM2 protein crystal structures, six drug molecules were identified as possible p53-MDM2 inhibitors.

Predicting targets of compounds against neurological diseases using cheminformatic methodology

Katarina Nikolic[University of Belgrade], Lazaros Mavridis, Oscar M. Bautista-Aguilera, José Marco-Contelles, Holger Stark, Maria do Carmo Carreiras, Ilaria Rossi, Paola Massarelli, Danica Agbaba, Rona R. Ramsay, John B. O. Mitchell

J.Comp.Aided. Mol.des. **29**, 183-198, 2015.

Recently developed multi-targeted ligands are novel drug candidates able to interact with monoamine oxidase A and B; acetylcholinesterase and butyrylcholinesterase; or with histamine *N*-methyltransferase and histamine H₃-receptor (H₃R). These proteins are drug targets in the treatment of depression, Alzheimer's disease, obsessive disorders, and Parkinson's disease. A probabilistic method, the Parzen–Rosenblatt window approach, was used to build a “predictor” model using data collected from the ChEMBL database. The model can be used to predict both the primary pharmaceutical target and off-targets of a compound based on its structure.

Prediction of Synthetic Accessibility Based on Commercially Available Compound Databases

Yoshifumi Fukunishi [National Institute of Advanced Industrial Science and Technology (AIST)], Takashi Kurosawa, Yoshiaki Mikami, Haruki Nakamura

J.Chem. Infor. and Mod. **54**, 3259–3267, 2014.

A compound's synthetic accessibility (SA) is an important aspect of drug design, since in some cases computer-designed compounds cannot be synthesized. There have been several reports on SA prediction, most of which have focused on the difficulties of synthetic reactions based on retro-synthesis analyses, reaction databases and the availability of starting materials. We developed a new method of predicting SA using commercially available compound databases and molecular descriptors. SA was estimated from the probability of existence of substructures consisting of the compound in question, the number of symmetry atoms, the graph complexity, and the number of chiral centers of the compound.

Medicinal Chemistry and Drug Design (Cont'd)

Binding Isotope Effects as a Tool for Distinguishing Hydrophobic and Hydrophilic Binding Sites of HIV-1 RT

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

J. Phys. Chem. B., **119**, 917–927, 2015.

The current treatment for HIV-1 infected patients consists of a cocktail of inhibitors, in an attempt to improve the potency of the drugs by adding the possible effects of each supplied compound. In this contribution, nine different inhibitors of HIV-1 RT, one of the three key proteins responsible for the virus replication, have been selected to develop and test a computational protocol that allows getting a deep insight into the inhibitors' binding mechanism. The interaction between the inhibitors and the protein have been quantified by computing binding free energies through FEP calculations, while a more detailed characterization of the kind of inhibitor–protein interactions is based on frequency analysis of the ligands in the initial and final state.

Experimental and Computational Prediction of Glass Transition Temperature of Drugs

Ahmad Alzghoul, Amjad Alhalaweh, Denny Mahlin, Christel A. S. Bergström [Uppsala University]

J.Chem. Infor. and Mod. **54**, 3396–3403, 2014.

Glass transition temperature (T_g) is an important inherent property of an amorphous solid material which is usually determined experimentally. In this study, the relation between T_g and melting temperature (T_m) was evaluated using a data set of 71 structurally diverse druglike compounds. Further, in silico models for prediction of T_g were developed based on calculated molecular descriptors and linear (multilinear regression, partial least-squares, principal component regression) and nonlinear (neural network, support vector regression) modeling techniques.

Thermodynamic Characterization of New Positive Allosteric Modulators Binding to the Glutamate Receptor A2 Ligand-Binding Domain: Combining Experimental and Computational Methods Unravels Differences in Driving Forces

Ann-Beth Nørholm, Pierre Francotte, Eric Goffin, Iuliana Botez, Laurence Danober, Pierre Lestage, Bernard Pirotte, Jette S. Kastrup, Lars Olsen, Chris Oostenbrink [University of Copenhagen]

J.Chem. Infor. and Mod. **54**, 3404–3416, 2014.

Positive allosteric modulation of the ionotropic glutamate receptor GluA2 presents a potential treatment of cognitive disorders, for example, Alzheimer's disease. In the present study, we describe the synthesis, pharmacology, and thermodynamic studies of a series of monofluoro-substituted 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides. Measurements of ligand binding by isothermal titration calorimetry (ITC) showed similar binding affinities for the modulator series at the GluA2 LBD but differences in the thermodynamic driving forces. Binding of 5c (7-F) and 6 (no-F) is enthalpy driven, and 5a (5-F) and 5b (6-F) are entropy driven. For 5d (8-F), both quantities were equal in size.

Computer-Aided Structure-Based Design of Multitarget Leads for Alzheimer's Disease

José L. Domínguez, Fernando Fernández-Nieto, Marian Castro, Marco Catto, M. Rita Paleo, Silvia Porto, F. Javier Sardina, José M. Brea, Angelo Carotti, M. Carmen Villaverde, Fredy Sussman [Universidad de Santiago de Compostela]

J.Chem. Infor. and Mod. **55**, 135–148, 2015.

Alzheimer's disease is a neurodegenerative pathology with unmet clinical needs. A highly desirable approach to this syndrome would be to find a single lead that could bind to some or all of the selected biomolecules that participate in the amyloid cascade, the most accepted route for Alzheimer disease genesis. In order to circumvent the challenge posed by the sizable differences in the binding sites of the molecular targets, we propose a computer-assisted protocol based on a pharmacophore and a set of required interactions with the targets that allows for the automated screening of candidates.

Medicinal Chemistry and Drug Design (Cont'd)

Biophysical Characteristics of Cholera Toxin and Escherichia coli Heat-Labile Enterotoxin Structure and Chemistry Lead to Differential Toxicity

John W. Craft, Jr., Tsai-wei Shen, Lindsey M. Brier, James M. Briggs [University of Houston]

J. Phys. Chem. B., **119**, 1048–1061, 2015.

The biophysical chemistry of macromolecular complexes confer their functional characteristics. We investigate the mechanisms that make the AB5 holotoxin of *Vibrio cholerae* (CT) a significantly more pathogenic molecule than the enterotoxin of *Escherichia coli* (LT) with which it shares 88% similarity and whose structure is homologous with a backbone RMSD of 0.84 Å and imposes its deleterious effects through the same process to constitutively ADP-ribosylate adenylate cyclase.

Hydrogen-Bonded Water Molecules in the M2 Channel of the Influenza A Virus Guide the Binding Preferences of Ammonium-Based Inhibitors

Eleonora Gianti, Vincenzo Carnevale, William F. DeGrado, Michael L. Klein [Temple University], Giacomo Fiorin

J. Phys. Chem. B., **119**, 1173–1183, 2015.

The tetrameric M2 proton channel of influenza A virus is an integral membrane protein responsible for the acidification of the viral interior. Drugs such as amantadine target the transmembrane region of wild type M2 by acting as pore blockers. However, a number of mutations affecting this domain confer drug resistance, prompting the need for alternative inhibitors. The availability of high-resolution structures of drug-bound M2, paired with computational investigations, revealed that inhibitors can bind at different sites, and provided useful insights in understanding the principles governing proton conduction.

Why Bound Amantadine Fails to Inhibit Proton Conductance According to Simulations of the Drug-Resistant Influenza A M2 (S31N)

Mitchell L. Glead, David D. Busath [Brigham Young University]

J. Phys. Chem. B., **119**, 1225–1231, 2015.

The mechanisms responsible for drug resistance in the Asn31 variant of the M2 protein of influenza A are not well understood. Molecular dynamics simulations were performed on wild-type (Ser31) and S31N influenza A M2 in the homotetramer configuration. After evaluation of 13 published M2 structures, a solid-state NMR structure with amantadine bound was selected for simulations, an S31N mutant structure was developed and equilibrated, and the native and mutant structures were used to determine the binding behavior of amantadine and the dynamics of water in the two channels.

Quantitative Structure-Activity Relations

Ligand-based modeling followed by in vitro bioassay yielded new potent glucokinase activators

Mutasem O. Taha [The University of Jordan], Maha Habash, Ma'mon M. Hatmal, Ahmed H. Abdelazeem, Amjad Qandil

J. Mol. Graph. and Mod., **56**, 91-102, 2015.

Glucokinase (GK) has received recent interest as a valid antidiabetic target. With this in mind, we applied a computational workflow based on combining pharmacophore modeling and QSAR analysis followed by in silico screening toward the discovery of novel GK activators. Virtual screening identified 10 promising bioactivators from the National Cancer Institute (NCI) list of compounds. The most potent NCI hit illustrated 6.3-fold GK activation at 10 µM. These results demonstrated that our virtual screening protocol was able to identify novel GK activator leads for subsequent development into potential antidiabetic agents.

QSAR (Cont'd)

Ligand-based 3D QSAR analysis of reactivation potency of mono- and bis-pyridinium aldoximes toward VX-inhibited rat acetylcholinesterase

Rafael Dolezal, Jan Korabecny, David Malinak, Jan Honegr, Kamil Musilek, Kamil Kuca [University Hospital Hradec Kralove]

J. Mol.Graph. and Mod., **56**,113-129,2015.

To predict unknown reactivation potencies of 12 mono- and bis-pyridinium aldoximes for VX-inhibited rat acetylcholinesterase (rAChE), three-dimensional quantitative structure–activity relationship (3D QSAR) analysis has been carried out. Utilizing molecular interaction fields (MIFs) calculated by molecular mechanical (MMFF94) and quantum chemical (B3LYP/6-31G*) methods, two satisfactory ligand-based CoMFA models have been developed. High statistical significance of the 3D QSAR models has been achieved through the application of several data noise reduction techniques (i.e. smart region definition SRD, fractional factor design FFD, uninformative/iterative variable elimination UVE/IVE) on the original MIFs.

Host-Guest Systems

Rationally Designed Cooperatively Enhanced Receptors To Magnify Host–Guest Binding in Water

Roshan W. Gunasekara , Yan Zhao [Iowa State University]

J. Am. Chem. Soc.,**137**, 843–849, 2015.

When disengaged interactions within a receptor are turned on by its guest, these intrahost interactions will contribute to the overall binding energy. Although such receptors are common in biology, their synthetic mimics are rare and difficult to design. By engineering conflictory requirements between intrareceptor electrostatic and hydrophobic interactions, we enabled complementary guests to eliminate the “electrostatic frustration” within the host and turn on the intrahost interactions. The result was a binding constant of $K_a > 10^5 \text{ M}^{-1}$ from ammonium–carboxylate salt bridges that typically function poorly in water.

Carbon Nanoparticles

Molecular dynamics simulation of melting and crystallization processes of polyethylene clusters confined in armchair single-walled carbon nanotubes

Zhou Zhou, Jinjian Wang, Xiaolei Zhu [Nanjing Tech University], Xiaohua Lu, Wenwen Guan, Yuchen Yang

J. Mol.Mod., **21**, 9, 2015.

The confined interaction is important to understand the melting and crystallization of polymers within single-wall carbon tube (SWNT). However, it is difficult for us to observe this interaction. In the current work, the structures and behaviors of melting and crystallization for polyethylene (PE) clusters confined in armchair single-walled carbon nanotubes ((n,n)-SWNTs) are investigated and examined based on molecular dynamics (MD) simulations. The nonbonded energies, structures, Lindemman indices, radial density distributions, and diffusion coefficients are used to demonstrate the features of melting phase transition for PE clusters confined in (n,n)-SWNTs.

Carbon Nanoparticles (Cont'd)

Encapsulation into Carbon Nanotubes and Release of Anticancer Cisplatin Drug Molecule

Alia Mejri, Delphine Vardanega, Bahoueddine Tangour, Tijani Gharbi, Fabien Picaud [Centre Hospitalier Universitaire et Université de Franche Comté]

J. Phys. Chem. B., **119**, 604–611, 2015.

Molecular dynamics simulations have been investigated to study the interactions between single-wall carbon nanotubes and an anticancer agent Pt complex (Cisplatin). The optimized diameter of the vector system has been determined to encapsulate in the best conditions the drug molecules. The simulation results show also that several drug molecules can be adsorbed inside the nanotubes, leading to an increased confinement time.

1.2. Biopolymers

Bioinformatics and Cheminformatics

ReaDDyMM: Fast Interacting Particle Reaction-Diffusion Simulations Using Graphical Processing Units

Johann Biedermann, Alexander Ullrich, Johannes Schöneberg, Frank Noé [Free University of Berlin]

Biophysical Journal. **108**, 457-461, 2015.

ReaDDy is a modular particle simulation package combining off-lattice reaction kinetics with arbitrary particle interaction forces. Here we present a graphical processing unit implementation of ReaDDy that employs the fast multiplatform molecular dynamics package OpenMM. A speedup of up to two orders of magnitude is demonstrated, giving us access to timescales of multiple seconds on single graphical processing units. This opens up the possibility of simulating cellular signal transduction events while resolving all protein copies.

iATTRACT: Simultaneous global and local interface optimization for protein–protein docking refinement

Christina E. M. Schindler, Sjoerd J. de Vries, Martin Zacharias [Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **83**, 248–258, 2015.

Protein-protein interactions are abundant in the cell but to date structural data for a large number of complexes is lacking. Computational docking methods can complement experiments by providing structural models of complexes based on structures of the individual partners. A major caveat for docking success is accounting for protein flexibility. Especially, interface residues undergo significant conformational changes upon binding. This limits the performance of docking methods that keep partner structures rigid or allow limited flexibility. A new docking refinement approach, iATTRACT, has been developed which combines simultaneous full interface flexibility and rigid body optimizations during docking energy minimization.

Bioinformatics and Cheminformatics (Cont'd)

CASP10-BCL::Fold efficiently samples topologies of large proteins

Sten Heinze, Daniel K. Putnam, Axel W. Fischer, Tim Kohlmann, Brian E. Weiner, Jens Meiler [Vanderbilt University]

Proteins: Stru. Fun. & Bioinf., **83**, 547–563, 2015.

During CASP10 in summer 2012, we tested BCL::Fold for prediction of free modeling (FM) and template-based modeling (TBM) targets. BCL::Fold assembles the tertiary structure of a protein from predicted secondary structure elements (SSEs) omitting more flexible loop regions early on. This approach enables the sampling of conformational space for larger proteins with more complex topologies. In preparation of CASP11, we analyzed the quality of CASP10 models throughout the prediction pipeline to understand BCL::Fold's ability to sample the native topology, identify native-like models by scoring and/or clustering approaches, and our ability to add loop regions and side chains to initial SSE-only models.

WESTPA: An Interoperable, Highly Scalable Software Package for Weighted Ensemble Simulation and Analysis

Matthew C. Zwier, Joshua L. Adelman, Joseph W. Kaus, Adam J. Pratt, Kim F. Wong, Nicholas B. Rego, Ernesto Suárez, Steven Lettieri, David W. Wang, Michael Grabe, Daniel M. Zuckerman, Lillian T. Chong [University of Pittsburgh]

J. Chem. Theor. and Comp., **11**, 800–809, 2015.

The weighted ensemble (WE) path sampling approach orchestrates an ensemble of parallel calculations with intermittent communication to enhance the sampling of rare events, such as molecular associations or conformational changes in proteins or peptides. Trajectories are replicated and pruned in a way that focuses computational effort on underexplored regions of configuration space while maintaining rigorous kinetics. To enable the simulation of rare events at any scale (e.g., atomistic, cellular), we have developed an open-source, interoperable, and highly scalable software package for the execution and analysis of WE simulations: WESTPA (The Weighted Ensemble Simulation Toolkit with Parallelization and Analysis). WESTPA scales to thousands of CPU cores and includes a suite of analysis tools that have been implemented in a massively parallel fashion.

Scaling Predictive Modeling in Drug Development with Cloud Computing

Behrooz Torabi Moghadam, Jonathan Alvarsson, Marcus Holm, Martin Eklund, Lars Carlsson, Ola Spjuth [Uppsala University]

J. Chem. Infor. and Mod. **55**, 19–25, 2015.

Growing data sets with increased time for analysis is hampering predictive modeling in drug discovery. Model building can be carried out on high-performance computer clusters, but these can be expensive to purchase and maintain. We have evaluated ligand-based modeling on cloud computing resources where computations are parallelized and run on the Amazon Elastic Cloud. We trained models on open data sets of varying sizes for the end points logP and Ames mutagenicity and compare with model building parallelized on a traditional high-performance computing cluster.

Bioinformatics and Cheminformatics (Cont'd)

Managing the Computational Chemistry Big Data Problem: The ioChem-BD Platform

M. Álvarez-Moreno, C. de Graaf, N. López, F. Maseras, J. M. Poblet, C. Bo [Universitat Rovira i Virgili]

J.Chem. Infor. and Mod. **55**, 95–103, 2015.

We present the ioChem-BD platform (www.iochem-bd.org) as a multiheaded tool aimed to manage large volumes of quantum chemistry results from a diverse group of already common simulation packages. The platform has an extensible structure. The key modules managing the main tasks are to (i) upload of output files from common computational chemistry packages, (ii) extract meaningful data from the results, and (iii) generate output summaries in user-friendly formats. A heavy use of the Chemical Mark-up Language (CML) is made in the intermediate files used by ioChem-BD.

Large-Scale Mining for Similar Protein Binding Pockets: With RAPMAD Retrieval on the Fly Becomes Real

Timo Krotzky, Christian Grunwald, Ute Egerland, Gerhard Klebe [Philipps-Universität Marburg]

J.Chem. Infor. and Mod. **55**, 165–179, 2015.

Determination of structural similarities between protein binding pockets is an important challenge in in silico drug design. It can help to understand selectivity considerations, predict unexpected ligand cross-reactivity, and support the putative annotation of function to orphan proteins. To this end, Cavbase was developed as a tool for the automated detection, storage, and classification of putative protein binding sites. In this study, we propose RAPMAD (RAPid Pocket MATCHing using Distances), a new evaluation formalism for Cavbase entries that allows for ultrafast similarity comparisons. Protein binding sites are represented by sets of distance histograms that are both generated and compared with linear complexity.

CoRILISA: A Local Similarity Based Receptor Dependent QSAR Method

Vijay M. Khedkar, Evans C. Coutinho [Bombay College of Pharmacy]

J.Chem. Infor. and Mod. **55**, 194–205, 2015.

Molecular similarity methods have played a crucial role in the success of structure-based and computer-assisted drug design. However, with the exception of CoMSIA, the current approaches for estimating molecular similarity yield a global picture thereby providing limited information about the local spatial molecular features responsible for the variation of activity with the 3D structure. Building on the ideas of our previously published methodologies—CoRIA and LISA, we present here a local molecular similarity based receptor dependent QSAR method termed CoRILISA which is a hybrid of the two approaches.

Multi-Conformer Ensemble Docking to Difficult Protein Targets

Sally R. Ellingson, Yinglong Miao, Jerome Baudry, Jeremy C. Smith [University of Tennessee]

J. Phys. Chem. B., **119**, 1026–1034, 2015.

Large-scale ensemble docking is investigated using five proteins from the Directory of Useful Decoys (DUD, dud.docking.org) for which docking to crystal structures has proven difficult. Molecular dynamics trajectories are produced for each protein and an ensemble of representative conformational structures extracted from the trajectories. Docking calculations are performed on these selected simulation structures and ensemble-based enrichment factors compared with those obtained using docking in crystal structures of the same protein targets or random selection of compounds.

Bioinformatics and Cheminformatics (Cont'd)

Pharmacophore-Based Similarity Scoring for DOCK

Lingling Jiang , Robert C. Rizzo [Stony Brook University]

J. Phys. Chem. B., **119**, 1083–1102 , 2015.

Pharmacophore modeling incorporates geometric and chemical features of known inhibitors and/or targeted binding sites to rationally identify and design new drug leads. In this study, we have encoded a three-dimensional pharmacophore matching similarity (FMS) scoring function into the structure-based design program DOCK. Validation and characterization of the method are presented through pose reproduction, crossdocking, and enrichment studies. When used alone, FMS scoring dramatically improves pose reproduction success to 93.5% (~20% increase) and reduces sampling failures to 3.7% (~6% drop) compared to the standard energy score (SGE) across 1043 protein–ligand complexes.

Internal Coordinate Molecular Dynamics: A Foundation for Multiscale Dynamics

Nagarajan Vaidehi, Abhinandan Jain [California Institute of Technology]

J. Phys. Chem. B., **119**, 1233–1242, 2015.

Internal coordinates such as bond lengths, bond angles, and torsion angles (BAT) are natural coordinates for describing a bonded molecular system. However, the molecular dynamics (MD) simulation methods that are widely used for proteins, DNA, and polymers are based on Cartesian coordinates owing to the mathematical simplicity of the equations of motion. However, constraints are often needed with Cartesian MD simulations to enhance the conformational sampling. Thus, the internal coordinate MD (ICMD) offers an attractive alternative to Cartesian coordinate MD for developing multiscale MD method. The torsional MD method is a special adaptation of the ICMD method, where all the bond lengths and bond angles are kept rigid.

Protein Secondary Structure

Secondary structure assignment for conformationally irregular peptides: Comparison between DSSP, STRIDE and KAKSI

Yuan Zhang, Celeste Sagui [North Carolina State University]

J. Mol. Graph. and Mod., **55**, 72-84, 2015.

Secondary structure assignment codes were built to explore the regularities associated with the periodic motifs of proteins, such as those in backbone dihedral angles or in hydrogen bonds between backbone atoms. In this work, we have carried out Molecular Dynamics simulations of (relatively) disordered peptides, specifically gp41_{659–671} (ELLELDKWASLWN), the homopeptide polyasparagine (N₁₈), and polyasparagine dimers. We have analyzed the resulting conformations with DSSP and STRIDE, based on hydrogen-bond patterns (and dihedral angles for STRIDE), and KAKSI, based on α -Carbon distances; and carefully characterized the differences in structural assignments.

Protein Secondary Structure (Cont'd)

Polymorphism in Self-Assembly of Peptide-Based β -Hairpin Contributes to Network Morphology and Hydrogel Mechanical Rigidity

Yifat Miller, Buyong Ma, Ruth Nussinov [Ben-Gurion University of the Negev]

J. Phys. Chem. B., **119**, 482–490, 2015.

Hydrogels are proving to be an excellent class of materials for biomedical applications. The molecular self-assembly of designed MAX1 β -hairpin peptides into fibrillar networks has emerged as a novel route to form responsive hydrogels. Herein, computational modeling techniques are used to investigate the relative arrangements of individual hairpins within the fibrils that constitute the gel. Our study suggests polymorphic arrangements of the hairpins within the fibrils; however, the relative populations and the relative conformational energies of the polymorphic arrangements show a preference toward an arrangement of hairpins where their turn regions are not capable of forming intermolecular interaction.

Mechanism of Stabilization of Helix Secondary Structure by Constrained C α -Tetrasubstituted α -Amino Acids

Irene Maffucci, Sara Pellegrino, Jonathan Clayden, Alessandro Contini [Università degli Studi di Milano]

J. Phys. Chem. B., **119**, 1350–1361, 2015.

The theoretical basis behind the ability of constrained C α -tetrasubstituted amino acids (CTAAs) to induce stable helical conformations has been studied through Replica Exchange Molecular Dynamics Potential of Mean Force Quantum Theory of Atoms In Molecules calculations on Ac-L-Ala-CTAA-L-Ala-Aib-L-Ala-NHMe peptide models. We found that the origin of helix stabilization by CTAAs can be ascribed to at least two complementary mechanisms limiting the backbone conformational freedom: steric hindrance predominantly in the (+x,+y,-z) sector of a right-handed 3D Cartesian space, where the z axis coincides with the helical axis and the C α of the CTAA lies on the +y axis (0,+y,0), and the establishment of additional and relatively strong C–H $\cdots$ O interactions involving the CTAA.

Protein Structure Prediction

PFP/ESG: automated protein function prediction servers enhanced with Gene Ontology visualization tool

Ishita K. Khan, Qing Wei, Meghana Chitale, Daisuke Kihara [Purdue University]

Bioinformatics. **30**, 271–272, 2015.

Protein function prediction (PFP) is an automated function prediction method that predicts Gene Ontology (GO) annotations for a protein sequence using distantly related sequences and contextual associations of GO terms. Extended similarity group (ESG) is another GO prediction algorithm that makes predictions based on iterative sequence database searches. Here, we provide interactive web servers for the PFP and ESG algorithms that are equipped with an effective visualization of the GO predictions in a hierarchical topology.

Protein Structure Prediction (Cont'd)

Exploring alternate states and oligomerization preferences of coiled-coils by de novo structure modeling

Sebastian Rämisch, Robert Lizatović ,Ingemar André[Lund University]

Proteins: Stru. Fun. & Bioinf., **83**, 235–247, 2015.

Homomeric coiled-coils can self-assemble into a wide range of structural states with different helix topologies and oligomeric states. In this study, we have combined de novo structure modeling with stability calculations to simultaneously predict structure and oligomeric states of homomeric coiled-coils. For dimers an asymmetric modeling protocol was developed. Modeling without symmetry constraints showed that backbone asymmetry is important for the formation of parallel dimeric coiled-coils. Collectively, our results demonstrate that high-resolution structure of coiled-coils, as well as parallel and antiparallel orientations of dimers and tetramers, can be accurately predicted from sequence.

Improving accuracy of protein contact prediction using balanced network deconvolution

Hai-Ping Sun, Yan Huang, Xiao-Fan Wang, Yang Zhang , Hong-Bin Shen [Shanghai Jiao Tong University]

Proteins: Stru. Fun. & Bioinf., **83**, 485–496, 2015.

Residue contact map is essential for protein three-dimensional structure determination. But most of the current contact prediction methods based on residue co-evolution suffer from high false-positives as introduced by indirect and transitive contacts (i.e., residues A–B and B–C are in contact, but A–C are not). Built on the work by Feizi et al. (Nat Biotechnol 2013; 31:726–733), which demonstrated a general network model to distinguish direct dependencies by network deconvolution, this study presents a new balanced network deconvolution (BND) algorithm to identify optimized dependency matrix without limit on the eigenvalue range in the applied network systems.

Comparative or Homology Modeling

PHI-DAC: protein homology database through dihedral angle conservation

Noa Maatuk, Yitav Glantz-Gashai, Maya Rotman, Meirav Baydany, Gennadiy Fonar, Amir Shechvitz, Karin Shemer, Aviva Peleg, Eli Reuveni, Abraham O. Samson[Bar Ilan University]

Bioinformatics. **30**, 292-294, 2015.

Finding related conformations in the Protein Data Bank is essential in many areas of bioscience. To assist this task, we designed a dihedral angle database for searching protein segment homologs. The search engine relies on encoding of the protein coordinates into text characters representing amino acid sequence, ϕ and ψ dihedral angles. The search engine is advantageous owing to its high speed and interactive nature and is expected to assist scientists in discovering conformation homologs and evolutionary kinship.

Comparative or Homology Modeling (Cont'd)

Homology models of the HIV-1 attachment inhibitor BMS-626529 bound to gp120 suggest a unique mechanism of action

David R. Langley [Bristol-Myers Squibb], S. Roy Kimura, Prasanna Sivaprakasam, Nannan Zhou, Ira Dicker, Brian McAuliffe, Tao Wang, John F. Kadow, Nicholas A. Meanwell, Mark Krystal

Proteins: Stru. Fun. & Bioinf., **83**, 331–350, 2015.

HIV-1 gp120 undergoes multiple conformational changes both before and after binding to the host CD4 receptor. BMS-626529 is an attachment inhibitor (AI) in clinical development (administered as prodrug BMS-663068) that binds to HIV-1 gp120. To investigate the mechanism of action of this new class of antiretroviral compounds, we constructed homology models of unliganded HIV-1 gp120 (UNLIG), a pre-CD4 binding-intermediate conformation (pCD4), a CD4 bound-intermediate conformation (bCD4), and a CD4/co-receptor-bound gp120 (LIG) from a series of partial structures. We also describe a simple pathway illustrating the transition between these four states.

Protein Conformational Analysis

Mechanism of the $\alpha\beta$ Conformational Change in F₁-ATPase after ATP Hydrolysis: Free-Energy Simulations

Yuko Ito [Yokohama City University], Mitsunori Ikeguchi

Biophysical Journal. **108**, 85-97, 2015.

One of the motive forces for F₁-ATPase rotation is the conformational change of the catalytically active β subunit due to closing and opening motions caused by ATP binding and hydrolysis, respectively. The closing motion is accomplished in two steps: the hydrogen-bond network around ATP changes and then the entire structure changes via B-helix sliding, as shown in our previous study. Here, we investigated the opening motion induced by ATP hydrolysis using all-atom free-energy simulations, combining the nudged elastic band method and umbrella sampling molecular-dynamics simulations. Because hydrolysis requires residues in the α subunit, the simulations were performed with the $\alpha\beta$ dimer.

Conformational Analysis of the DFG-Out Kinase Motif and Biochemical Profiling of Structurally Validated Type II Inhibitors

R. S. K. Vijayan, Peng He, Vivek Modi, Krisna C. Duong-Ly, Haiching Ma, Jeffrey R. Peterson, Roland L. Dunbrack, Jr., Ronald M. Levy [Temple University, Philadelphia]

J. Med. Chem., **58**, 466–479, 2015.

Structural coverage of the human kinome has been steadily increasing over time. The structures provide valuable insights into the molecular basis of kinase function and also provide a foundation for understanding the mechanisms of kinase inhibitors. We have completed a structural analysis of almost 200 small molecule inhibitors bound to classical DFG-out conformations; we find that they are recognized by both type I and type II inhibitors. In contrast, we find that nonclassical DFG-out conformations strongly select against type II inhibitors because these structures have not formed a large enough allosteric pocket to accommodate this type of binding mode.

Protein Conformational Analysis (Cont'd)

Principal Component Analysis reveals correlation of cavities evolution and functional motions in proteins

Nathan Desdouits [Institut Pasteur, CNRS - UMR3258],
Michael Nilges, Arnaud Blondel

J. Mol.Graph. and Mod., **55**,13-24,2015.

Protein conformation has been recognized as the key feature determining biological function, as it determines the position of the essential groups specifically interacting with substrates. Hence, the shape of the cavities or grooves at the protein surface appears to drive those functions. However, only a few studies describe the geometrical evolution of protein cavities during MD simulations, usually with a crude representation. To unveil the dynamics of cavity geometry evolution, we developed an approach combining cavity detection and Principal Component Analysis (PCA).

Sparse networks of directly coupled, polymorphic, and functional side chains in allosteric proteins

Laleh Soltan Ghoraie [University of Waterloo], Forbes Burkowski, Mu Zhu

Proteins: Stru. Fun. & Bioinf., **83**, 497–516, 2015.

Recent studies have highlighted the role of coupled side-chain fluctuations alone in the allosteric behavior of proteins. Moreover, examination of X-ray crystallography data has recently revealed new information about the prevalence of alternate side-chain conformations (conformational polymorphism), and attempts have been made to uncover the hidden alternate conformations from X-ray data. In this article, we first present a novel approach to generate an ensemble of conformations and an efficient computational method to extract direct couplings of side chains in allosteric proteins, and provide sparse network representations of the couplings.

Accuracy of Current All-Atom Force-Fields in Modeling Protein Disordered States

Ferruccio Palazzesi[Università della Svizzera Italiana], Meher K. Prakash, Massimiliano Bonomi, Alessandro Barducci

J. Chem. Theor. and Comp., **11**, 2–7, 2015.

Molecular Dynamics (MD) plays a fundamental role in characterizing protein disordered states that are emerging as crucial actors in many biological processes. Here we assess the accuracy of three current force-fields in modeling disordered peptides by combining enhanced-sampling MD simulations with NMR data. These force-fields generate significantly different conformational ensembles, and AMBER03w [Best and Mittal *J. Phys. Chem. B* 2010,114, 14916–14923] provides the best agreement with experiments, which is further improved by adding the ILDN corrections [Lindorff-Larsen et al. *Proteins* 2010, 78, 1950–1958].

Conformational Sampling of Oligosaccharides Using Hamiltonian Replica Exchange with Two-Dimensional Dihedral Biasing Potentials and the Weighted Histogram Analysis Method (WHAM)

Mingjun Yang, Alexander D. MacKerell, Jr. [University of Maryland]

J. Chem. Theor. and Comp., **11**, 788–799, 2015.

Oligosaccharides and polysaccharides exert numerous functional roles in biology through their structural diversity and conformational properties. To investigate their conformational properties using computational methods, Hamiltonian replica exchange (H-REX) combined with two-dimensional grid-based correction maps as biasing potentials (bpCMAP) significantly improves the sampling efficiency about glycosidic linkages. In the current study, we extend the application of H-REX with bpCMAP to complex saccharides and establish systematic procedures for bpCMAP construction, determination of replica distribution, and data analysis.

Protein Conformational Analysis (Cont'd)

Predicting Protein Backbone Chemical Shifts From Ca Coordinates: Extracting High Resolution Experimental Observables from Low Resolution Models

Aaron T. Frank, Sean M. Law, Logan S. Ahlstrom, Charles L. Brooks, III [University of Michigan]

J. Chem. Theor. and Comp., **11**, 325–331, 2015.

Given the demonstrated utility of coarse-grained modeling and simulations approaches in studying protein structure and dynamics, developing methods that allow experimental observables to be directly recovered from coarse-grained models is of great importance. In this work, we develop one such method that enables protein backbone chemical shifts (^1HN , ^1Ha , ^{13}Ca , ^{13}C , $^{13}\text{C}\beta$, and ^{15}N) to be predicted from Ca coordinates. We show that our Ca -based method, LARMOR Ca , predicts backbone chemical shifts with comparable accuracy to some all-atom approaches.

Physics-Based Potentials for the Coupling between Backbone- and Side-Chain-Local Conformational States in the United Residue (UNRES) Force Field for Protein Simulations

Adam K. Sieradzan, Paweł Krupa [University of Gdańsk], Harold A. Scheraga, Adam Liwo, Cezary Czaplewski

J. Chem. Theor. and Comp., **11**, 817–831, 2015.

The UNited RESidue (UNRES) model of polypeptide chains is a coarse-grained model in which each amino-acid residue is reduced to two interaction sites, namely, a united peptide group (p) located halfway between the two neighboring α -carbon atoms (Ca s), which serve only as geometrical points, and a united side chain (SC) attached to the respective Ca . In this work, we introduce the physics-based counterparts of these potentials, which we derived from the all-atom energy surfaces of terminally blocked amino-acid residues by Boltzmann integration over the angles $\lambda(1)$ and $\lambda(2)$ for rotation about the $\text{Ca}\cdots\text{Ca}$ virtual-bond angles and over the side-chain angles χ .

Determination of Conformational Entropy of Fully and Partially Folded Conformations of Holo- and Apomyoglobin

Andreas M. Stadler [Jülich Centre for Neutron Science JCNS and Institute for Complex Systems], Michael Marek Koza, Jörg Fitter

J. Phys. Chem. B., **119**, 72–82, 2015.

Holo- and apomyoglobin can be stabilized in native folded, partially folded molten globules (MGs) and denatured states depending on the solvent composition. Although the protein has been studied as a model system in the field of protein folding, little is known about the internal dynamics of the different structural conformations on the picosecond time scale. In a comparative experimental study we investigated the correlation between protein folding and dynamics on the picosecond time scale using incoherent quasielastic neutron scattering (QENS).

Assessing the Suitability of the Multilevel Strategy for the Conformational Analysis of Small Ligands

Jordi Juárez-Jiménez, Xavier Barril, Modesto Orozco, Ramon Pouplana, F. Javier Luque [Universitat de Barcelona]

J. Phys. Chem. B., **119**, 1164–1172, 2015.

Predicting the conformational preferences of flexible compounds is a challenging problem in drug design, where the recognition between ligand and receptor is affected by the ability of the interacting partners to adopt a favorable conformation for the binding. To explore the conformational space of flexible ligands and to obtain the relative free energy of the conformation wells, we have recently reported a multilevel computational strategy that relies on the predominant-state approximation—where the conformational space is partitioned into distinct conformational wells—and combines a low-level method for sampling the conformational minima and high-level ab initio calculations for estimating their relative stability.

Protein Conformational Analysis (Cont'd)

Probing Structural Determinants of ATP-Binding Cassette Exporter Conformational Transition Using Coarse-Grained Molecular Dynamics

Zi Wang , Jie-Lou Liao [University of Science and Technology of China]

J. Phys. Chem. B., **119**, 1295–1301, 2015.

ATP-binding cassette (ABC) exporters pump various substrates across the cell membrane by alternating between inward-facing (IF) and outward-facing (OF) conformations of the transmembrane domains (TMDs). However, the structural determinants of the conformational transition and their functional roles are not fully understood. In this study, we carried out coarse-grained molecular dynamics (CG-MD) simulations with umbrella sampling for the multidrug transporter P-glycoprotein from *Caenorhabditis elegans* in the presence of the membrane and explicit water molecules.

A Structural Mechanism for Calcium Transporter Headpiece Closure

Nikolai Smolin , Seth L. Robia [Loyola University Chicago]

J. Phys. Chem. B., **119**, 1407–1415, 2015.

To characterize the conformational dynamics of sarcoplasmic reticulum (SR) calcium pump (SERCA) we performed molecular dynamics simulations beginning with several different high-resolution structures. We quantified differences in structural disorder and dynamics for an open conformation of SERCA versus closed structures and observed that dynamic motions of SERCA cytoplasmic domains decreased with decreasing domain–domain separation distance. The results are useful for interpretation of recent intramolecular Förster resonance energy transfer (FRET) distance measurements obtained for SERCA fused to fluorescent protein tags.

Computational Study of the “DFG-Flip” Conformational Transition in c-Abl and c-Src Tyrosine Kinases

Yilin Meng, Yen-lin Lin, Benoît Roux [The University of Chicago]

J. Phys. Chem. B., **119**, 1443–1456, 2015.

Protein tyrosine kinases are crucial to cellular signaling pathways regulating cell growth, proliferation, metabolism, differentiation, and migration. To maintain normal regulation of cellular signal transductions, the activities of tyrosine kinases are also highly regulated. The conformation of a three-residue motif Asp-Phe-Gly (DFG) near the N-terminus of the long “activation” loop covering the catalytic site is known to have a critical impact on the activity of c-Abl and c-Src tyrosine kinases. In the present study, the string method with swarms-of-trajectories was used to computationally determine the reaction pathway connecting the two end-states, and umbrella sampling calculations were carried out to characterize the thermodynamic factors affecting the conformations of the DFG motif in c-Abl and c-Src kinases.

Protein Structure Analysis

pmx: Automated protein structure and topology generation for alchemical perturbations

Vytautas Gapsys [Max Planck Institute for Biophysical Chemistry, Göttingen], Servaas Michielssens, Daniel Seeliger, Bert L. de Groot

J. Comp. Chem., **36**, 348–354, 2015.

Computational protein design requires methods to accurately estimate free energy changes in protein stability or binding upon an amino acid mutation. From the different approaches available, molecular dynamics-based alchemical free energy calculations are unique in their accuracy and solid theoretical basis. The challenge in using these methods lies in the need to generate hybrid structures and topologies representing two physical states of a system.

Ab initio modeling approach towards establishing the structure and docking orientation of the Porphyromonas gingivalis FimA

Marni E. Cueno [Nihon University], Keiji Nagano, Kenichi Imai, Muneaki Tamura, Fuminobu Yoshimura, Kuniyasu Ochiai

J. Mol.Graph. and Mod., **55**, 65-71,2015.

Porphyromonas gingivalis FimA is a major aetiological agent in periodontal disease development, however, its structure has never been determined. Here, we established the mature P. gingivalis FimA ab initio model of all six FimA variants. We determined the conserved amino acid sequences of each FimA variant and generated mature FimA models. Subsequently, we validated their quality, protein empirical distribution, and radius of gyration. Similarly, structural comparison and topological orientation were elucidated, and the probable protein–protein docking was investigated.

An approach to creating a more realistic working model from a protein data bank entry

Christopher J. Brandon [University of Colorado], Benjamin P. Martin, Kelly J. McGee, James J. P. Stewart, Sonja B. Braun-Sand

J. Mol.Mod., **21**, 3, 2015.

An accurate model of three-dimensional protein structure is important in a variety of fields such as structure-based drug design and mechanistic studies of enzymatic reactions. While the entries in the Protein Data Bank (<http://www.pdb.org>) provide valuable information about protein structures, a small fraction of the PDB structures were found to contain anomalies not reported in the PDB file. The semiempirical PM7 method in MOPAC2012 was used for identifying anomalously short hydrogen bonds, C–H···O/C–H···N interactions, non-bonding close contacts, and unrealistic covalent bond lengths in recently published Protein Data Bank files.

MaxMod: a hidden Markov model based novel interface to MODELLER for improved prediction of protein 3D models

Bikram K. Parida, Prasanna K. Panda [CSIR-Institute of Minerals & Materials Technology], Namrata Misra, Barada K. Mishra

J. Mol.Mod., **21**, 30, 2015.

Modeling the three-dimensional (3D) structures of proteins assumes great significance because of its manifold applications in biomolecular research. Toward this goal, we present MaxMod, a graphical user interface (GUI) of the MODELLER program that combines profile hidden Markov model (profile HMM) method with Clustal Omega program to significantly improve the selection of homologous templates and target-template alignment for construction of accurate 3D protein models. MaxMod distinguishes itself from other existing GUIs of MODELLER software by implementing effortless modeling of proteins using templates that bear modified residues.

Protein Dynamics

Simulations Show that Virus Assembly and Budding Are Facilitated by Membrane Microdomains

Teresa Ruiz-Herrero, Michael F. Hagan[Brandeis University]

Biophysical Journal. **108**, 585-595, 2015.

For many viruses, assembly and budding occur simultaneously during virion formation. Understanding the mechanisms underlying this process could promote biomedical efforts to block viral propagation and enable use of capsids in nanomaterials applications. To this end, we have performed molecular dynamics simulations on a coarse-grained model that describes virus assembly on a fluctuating lipid membrane. Our simulations show that the membrane can promote association of adsorbed subunits through dimensional reduction, but it also introduces thermodynamic and kinetic effects that can inhibit complete assembly.

Exploring the Scaffold Universe of Kinase Inhibitors

Ye Hu , Jürgen Bajorath [Rheinische Friedrich-Wilhelms-Universität]

J.Med.Chem., **58**, 315–332, 2015.

The scaffold concept was applied to systematically determine, analyze, and compare core structures of kinase inhibitors. From publicly available inhibitors of the human kinome, scaffolds and cyclic skeletons were systematically extracted and organized taking activity data, structural relationships, and retrosynthetic criteria into account. Scaffold coverage varied greatly across the kinome, and many scaffolds representing compounds with different activity profiles were identified.

Cloning and molecular modeling of a thermostable carboxylesterase from the chicken uropygial glands

Ahmed Fendri[Laboratoire de Biochimie et de Génie Enzymatique des Lipases], Fakher Frikha, Hanen Louati, Madiha Bou Ali, Hela Gargouri, Youssef Gargouri, Nabil Miled

J. Mol.Graph. and Mod., **56**,1-9,2015.

Starting from total uropygial glands mRNAs, chicken uropygial carboxylesterase (cuCES) cDNA was synthesized by RT-PCR and cloned into the PGEM-T vector. Amino acid sequence of the cuCES is compared to that of human liver carboxylesterase 1 (hCES1). Given the high amino acid sequence homology between the two enzymes, a 3-D structure model of the chicken carboxylesterase was built using the structure of hCES1 as template. By following this model and utilizing molecular dynamics (MD) simulations, the resistance of the chicken carboxylesterase at high temperatures could be explained.

Carboxyl–Peptide Plane Stacking Is Important for Stabilization of Buried E305 of *Trichoderma reesei* Cel5A

Chunyan He, Jingfei Chen, Liaoyuan An, Yefei Wang, Zhiyu Shu, Lishan Yao[Chinese Academy of Sciences]

J.Chem. Infor. and Mod. **55**, 104–113, 2015.

Hydrogen bonds or salt bridges are usually formed to stabilize the buried ionizable residues. However, such interactions do not exist for two buried residues D271 and E305 of *Trichoderma reesei* Cel5A, an endoglucanase. Mutating D271 to alanine or leucine improves the enzyme thermostability quantified by the temperature T50 due to the elimination of the desolvation penalty of the aspartic acid. However, the same mutations for E305 decrease the enzyme thermostability. Free energy calculations based on the molecular dynamics simulation predict the thermostability of D271A, D271L, and E305A (compared to WT) in line with the experimental observation but overestimate the thermostability of E305L.

Protein Dynamics (Cont'd)

Computer Simulation Studies of A β 37–42 Aggregation Thermodynamics and Kinetics in Water and Salt Solution

Y. Isaac Yang, Yi Qin Gao [Peking University]

J. Phys. Chem. B., **119**, 662–670, 2015.

In vivo self-assembly of proteins into aggregates known as amyloids is related to many diseases. Although a large number of studies have been performed on the formation of amyloid, the molecular mechanism of polypeptide aggregation remains largely unclear. In this paper, we studied the aggregation of amyloid-forming peptide A β 37–42 using all-atom molecular dynamics simulations. Using the integrated temperature sampling (ITS) simulation method, we observed the reversible formation of A β 37–42 oligomers. The free-energy landscape for the polypeptide association was calculated, and aggregated states were then defined based on the landscape.

Charge-Induced Patchy Attractions between Proteins

Weimin Li, Björn A. Persson, Maxim Morin, Manja A. Behrens, Mikael Lund, Malin Zackrisson Oskolkova [Lund University]

J. Phys. Chem. B., **119**, 503–508, 2015.

Static light scattering (SLS) combined with structure-based Monte Carlo (MC) simulations provide new insights into mechanisms behind anisotropic, attractive protein interactions. A nonmonotonic behavior of the osmotic second virial coefficient as a function of ionic strength is here shown to originate from a few charged amino acids forming an electrostatic attractive patch, highly directional and complementary. Together with Coulombic repulsion, this attractive patch results in two counteracting electrostatic contributions to the interaction free energy which, by operating over different length scales, is manifested in a subtle, salt-induced minimum in the second virial coefficient as observed in both experiment and simulations.

Protocols Utilizing Constant pH Molecular Dynamics to Compute pH-Dependent Binding Free Energies

M. Olivia Kim, Patrick G. Blachly, Joseph W. Kaus, J. Andrew McCammon [University of California San Diego]

J. Phys. Chem. B., **119**, 861–872, 2015.

In protein–ligand binding, the electrostatic environments of the two binding partners may vary significantly in bound and unbound states, which may lead to protonation changes upon binding. In cases where ligand binding results in a net uptake or release of protons, the free energy of binding is pH-dependent. Nevertheless, conventional free energy calculations and molecular docking protocols typically do not rigorously account for changes in protonation that may occur upon ligand binding.

Disentangling Volumetric and Hydrational Properties of Proteins

Vladimir P. Voloshin, Nikolai N. Medvedev, Nikolai Smolin, Alfons Geiger, Roland Winter [Technische Universität Dortmund]

J. Phys. Chem. B., **119**, 1881–1890, 2015.

We used molecular dynamics simulations of a typical monomeric protein, SNase, in combination with Voronoi–Delaunay tessellation to study and analyze the temperature dependence of the apparent volume, V_{app} , of the solute. We show that the void volume, V_B , created in the boundary region between solute and solvent, determines the temperature dependence of V_{app} to a major extent. The less pronounced but still significant temperature dependence of the molecular volume of the solute, V_M , is essentially the result of the expansivity of its internal voids, as the van der Waals contribution to V_M is practically independent of temperature.

Protein Dynamics (Cont'd)

Molecular Insights into the Role of Aqueous Trehalose Solution on Temperature-Induced Protein Denaturation

Subrata Paul , Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **119**, 1598–1610, 2015.

To investigate the underlying mechanism by which trehalose acts as a bioprotectant against thermal denaturation of protein in aqueous solution, we carry out classical molecular dynamics simulations at two different temperatures. Though it is widely accepted that trehalose acts as an antidote against such protein structural destabilization and numerous hypotheses have been proposed in regard to its mechanism of stabilization, there is still no definitive generally accepted answer to this question and it remains a subject of active research. In view of this, in this article we report the thermal denaturation process of a 15-residue S-peptide analogue at 360 K temperature and the counteracting ability of trehalose of varying concentrations at that temperature.

Energy Propagation and Network Energetic Coupling in Proteins

Andre A. S. T. Ribeiro ,Vanessa Ortiz [Columbia University]

J. Phys. Chem. B., **119**, 1835–1846, 2015.

Understanding how allosteric proteins respond to changes in their environment is a major goal of current biological research. We show that these responses can be quantified by analyzing protein energy networks using a method recently developed in our group. On the basis of this method, we introduce here a quantity named energetic coupling, which we show is able to discriminate allosterically active mutants of the lactose repressor (LacI) protein, and of the catabolite activator protein (CAP), a dynamically driven allosteric protein. Our method assumes that allostery and signal transmission can be more accurately described as efficient energy propagation, and not as the more widely used atomic motion correlations.

A Computational Study of the Effect of Matrix Structural Order on Water Sorption by Trp-Cage Miniproteins

Sang Beom Kim, Jeremy C. Palmer, Pablo G. Debenedetti [Princeton University]

J. Phys. Chem. B., **119**, 1847–1856, 2015.

We present the first simulation study of the impact of protein matrix structure on water sorption along with a new computational method to hydrate and dehydrate protein systems reversibly. To understand the impact of the underlying structure of the protein matrix on the hydration process, we compare three types of protein substrates comprised of Trp-cage miniproteins with varying degrees of monomer translational and orientational order and monomer denaturation. We show that the water sorption isotherms are qualitatively and quantitatively very similar for the Trp-cage matrices independently of the underlying degree of disorder, which is consistent with the experimental observation that the qualitative features of water sorption isotherms are nearly universal for globular proteins.

Protein Dynamics (Cont'd)

Motions and Entropies in Proteins as Seen in NMR Relaxation Experiments and Molecular Dynamics Simulations

Olof Allnér, Nicolas Foloppe, Lennart Nilsson[Karolinska Institutet]

J. Phys. Chem. B., **119**, 1114–1128, 2015.

Molecular dynamics simulations of E. coli glutaredoxin1 in water have been performed to relate the dynamical parameters and entropy obtained in NMR relaxation experiments, with results extracted from simulated trajectory data. NMR relaxation is the most widely used experimental method to obtain data on dynamics of proteins, but it is limited to relatively short timescales and to motions of backbone amides or in some cases ^{13}C –H vectors. By relating the experimental data to the all-atom picture obtained in molecular dynamics simulations, valuable insights on the interpretation of the experiment can be gained.

Free Energy Calculations

Finite-Size Effect on the Charging Free Energy of Protein in Explicit Solvent

Toru Ekimoto, Nobuyuki Matubayasi, Mitsunori Ikeguchi [Yokohama City University]

J. Chem. Theor. and Comp., **11**, 215–223, 2015.

The finite-size effect in periodic system is examined for the charging free energy of protein in explicit solvent over a variety of charged states. The key to the finite-size correction is the self-energy, which is defined as the interaction energy of the solute with its own periodic images and the neutralizing background. By employing the thermodynamic-integration method with systematically varied sizes of the unit cell of MD simulations, we show for ubiquitin that the self-energy corrects the finite-size effect on the charging free energy within 1 kcal/mol at total charges of $-5e$, $-1e$, neutral, and $+1e$ and within 5 kcal/mol even for a highly charged state with $+8e$.

Free Energies from Dynamic Weighted Histogram Analysis Using Unbiased Markov State Model

Edina Rosta [Max Planck Institute of Biophysics], Gerhard Hummer

J. Chem. Theor. and Comp., **11**, 276–285, 2015.

The weighted histogram analysis method (WHAM) is widely used to obtain accurate free energies from biased molecular simulations. However, WHAM free energies can exhibit significant errors if some of the biasing windows are not fully equilibrated. To account for the lack of full equilibration, we develop the dynamic histogram analysis method (DHAM). DHAM uses a global Markov state model to obtain the free energy along the reaction coordinate. A maximum likelihood estimate of the Markov transition matrix is constructed by joint unbiasing of the transition counts from multiple umbrella-sampling simulations along discretized reaction coordinates.

Free Energy Calculations (Cont'd)

Efficient Nonequilibrium Method for Binding Free Energy Calculations in Molecular Dynamics Simulations

Robert B. Sandberg, Martina Banchelli, Carlo Guardiani, Stefano Menichetti, Gabriella Caminati, Piero Procacci [University of Florence]

J. Chem. Theor. and Comp., **11**, 423–435, 2015.

We introduce an effective technique for the calculation of the binding free energy in drug-receptor systems using nonequilibrium molecular dynamics and application of the Jarzynski theorem. In essence, this novel methodology constitutes the nonequilibrium adaptation of an ancient free energy perturbation technique called Double Annihilation Method, invented more than 25 years ago [*J. Chem. Phys.* 1988, 89, 3742–3746] and upon which modern approaches of binding free energy computation in drug-receptor systems are heavily based.

Ligand Binding/Docking

Docking model of the nicotinic acetylcholine receptor and nitromethylene neonicotinoid derivatives with a longer chiral substituent and their biological activities

Hikaru Nagaoka, Hisashi Nishiwaki [Ehime University], Takuya Kubo, Miki Akamatsu, Satoshi Yamauchi, Yoshihiro Shuto

Bioorg. and Med.Chem., **23**, 759-769, 2015.

In the present study, nitromethylene neonicotinoid derivatives possessing substituents that contain a sulfur atom, oxygen atom or aromatic ring at position 5 on the imidazolidine ring were synthesized to evaluate their affinity for the nicotinic acetylcholine receptor (nAChR) and their insecticidal activity against adult female houseflies. Comparing the receptor affinity of the alkylated derivative with the receptor affinity of compounds possessing either ether or thioether groups revealed that conversion of the carbon atom to a sulfur atom did not influence the receptor affinity, whereas conversion to an oxygen atom was disadvantageous for the receptor affinity.

Iterative Conversion of Cyclin Binding Groove Peptides into Druglike CDK Inhibitors with Antitumor Activity

Padmavathy Nandha Premnath, Sandra N. Craig, Shu Liu, Erin L. Anderson, Asterios I. Grigoroudis, George Kontopidis, Tracy L. Perkins, Michael D. Wyatt, Douglas L. Pittman, Campbell McInnes [University of South Carolina]

J.Med.Chem., **58**, 433–442, 2015.

The cyclin groove is an important recognition site for substrates of the cell cycle cyclin dependent kinases and provides an opportunity for highly selective inhibition of kinase activity through a non-ATP competitive mechanism. The key peptide residues of the cyclin binding motif have been studied in order to precisely define the structure–activity relationship for CDK kinase inhibition. Through this information, new insights into the interactions of peptide CDK inhibitors with key subsites of the cyclin binding groove provide for the replacement of binding determinants with more druglike functionality through REPLACE, a strategy for the iterative conversion of peptidic blockers of protein–protein interactions into pharmaceutically relevant compounds.

Ligand Binding / Docking (Cont'd)

Imidacloprid and thiacloprid neonicotinoids bind more favourably to cockroach than to honeybee $\alpha 6$ nicotinic acetylcholine receptor: Insights from computational studies

Balaji Selvam [Université de Nantes], Jérôme Graton, Adèle D. Laurent, Zakaria Alamiddine, Monique Mathé-Allainmat, Jacques Lebreton, Olivier Coqueret, Christophe Olivier, Steeve H. Thany, Jean-Yves Le Questel

J. Mol.Graph. and Mod., **55**,1-12,2015.

The binding interactions of two neonicotinoids, imidacloprid (IMI) and thiacloprid (THI) with the extracellular domains of cockroach and honeybee $\alpha 6$ nicotinic acetylcholine receptor (nAChR) subunits in an homomeric receptor have been studied through docking and molecular dynamics (MD) simulations. The binding mode predicted for the two neonicotinoids is validated through the good agreement observed between the theoretical results with the crystal structures of the corresponding complexes with Ac-AChBP, the recognized structural surrogate for insects nAChR extracellular ligand binding domain. The binding site of the two insect $\alpha 6$ receptors differs by only one residue of loop D, a serine residue (Ser83) in cockroach being replaced by a lysine residue (Lys108) in honeybee.

Molecular dynamics simulation and free energy calculation studies of kinase inhibitors binding to active and inactive conformations of VEGFR-2

XiaoYun Wu, ShanHe Wan, GuangFa Wang, Hong Jin, ZhongHuang Li, YuanXin Tian, ZhengGuang Zhu, JiaJie Zhang[Southern Medical University]

J. Mol.Graph. and Mod., **56**,103-112,2015.

Vascular endothelial growth factors receptor-2 (VEGFR-2) inhibitors have been proved as very effective anticancer agents. Structurally similar ligands **1** and **2** show almost the same inhibitory activities against VEGFR-2, but they bind to the enzyme in distinct binding mode. Ligand **1** targets DFG-in active conformation of VEGFR-2, known as Type I inhibitor. On the other hand, ligand **2** targets DFG-out inactive conformation of VEGFR-2, known as Type II inhibitor or allosteric kinase inhibitor. In this work, molecular dynamics simulations and free energy calculations were performed on inhibitors **1–3** binding to active and inactive conformation of VEGFR-2.

Common functionally important motions of the nucleotide-binding domain of Hsp70

Ewa I. Gołaś, Cezary Czaplewski, Harold A. Scheraga ,Adam Liwo[University of Gdańsk]

Proteins: Stru. Fun. & Bioinf., **83**, 282–299, 2015.

The 70 kDa heat shock proteins (Hsp70) are a family of molecular chaperones involved in protein folding, aggregate prevention, and protein disaggregation. They consist of the substrate-binding domain (SBD) that binds client substrates, and the nucleotide-binding domain (NBD), whose cycles of nucleotide hydrolysis and exchange underpin the activity of the chaperone. To characterize the structure–function relationships that link the binding state of the NBD to its conformational behavior, we analyzed the dynamics of the NBD of the Hsp70 chaperone from *Bos taurus* (PDB 3C7N:B) by all-atom canonical molecular dynamics simulations.

Ligand Binding / Docking (Cont'd)

Characterization of the differences in the cyclopiazonic acid binding mode to mammalian and *P. Falciparum* Ca²⁺ pumps: A computational study

Daniele Di Marino, Ilda D'Annessa, Andrea Coletta, Allegra Via [Sapienza University] , Anna Tramontano

Proteins: Stru. Fun. & Bioinf., **83**, 564–574, 2015.

Despite the INVESTMENTS in malaria research, an effective vaccine has not yet been developed and the causative parasites are becoming increasingly resistant to most of the available drugs. PfATP6, the sarco/endoplasmic reticulum Ca²⁺ pump (SERCA) of *P. falciparum*, has been recently genetically validated as a potential antimalarial target and cyclopiazonic acid (CPA) has been found to be a potent inhibitor of SERCAs in several organisms, including *P. falciparum*. In position 263, PfATP6 displays a leucine residue, whilst the corresponding position in the mammalian SERCA is occupied by a glutamic acid. The PfATP6 L263E mutation has been studied in relation to the artemisinin inhibitory effect on *P. falciparum* and recent studies have provided evidence that the parasite with this mutation is more susceptible to CPA.

Intermediate states in the binding process of folic acid to folate receptor α : insights by molecular dynamics and metadynamics

Stefano Della-Longa [Università dell'Aquila], Alessandro Arcovito

J.Comp.Aided. Mol.des. **29**, 23-35, 2015.

Folate receptor α (FR α) is a cell surface, glycoposphatidylinositol-anchored protein which has focussed attention as a therapeutic target and as a marker for the diagnosis of cancer. It has a high affinity for the dietary supplemented folic acid (FOL), carrying out endocytic transport across the cell membrane and delivering the folate at the acidic pH of the endosome. Starting from the recently reported X-ray structure at pH 7, 100 ns classical molecular dynamics simulations have been carried out on the FR α -FOL complex; moreover, the ligand dissociation process has been studied by metadynamics, a recently reported method for the analysis of free-energy surfaces (FES), providing clues on the intermediate states and their energy terms.

Insight into the modified Ibalizumab–human CD4 receptor interactions: using a computational binding free energy approach

Yeng-Tseng Wang [Kaohsiung Medical University] , Lea-Yea Chuang

J.Comp.Aided. Mol.des. **29**, 69-78, 2015.

Antibody drugs are very useful tools for the treatment of many chronic diseases. Recently, however, patients and doctors have encountered the problem of drug resistance. This study investigates the mutation residues of the complementarity determining regions of Ibalizumab. We propose using the wild and mutations of Ibalizumab–human CD4 receptor complex structures, molecular dynamics techniques, alanine-scanning mutagenesis calculations and solvated interaction energies methods to predict the binding free energy of the Ibalizumab–human CD4 receptor complex structures.

Ligand Binding / Docking (Cont'd)

Structural Insight into the Unique Binding Properties of Pyridylethanol(phenylethyl)amine Inhibitor in Human CYP51

Urška Zelenko, Milan Hodošek, Damjana Rozman, Simona Golič Grdadolnik [National Institute of Chemistry, Hajdrihova 19]

J.Chem. Infor. and Mod. **54**, 3384–3395, 2014.

Sterol 14 α -demethylase (CYP51) is the main drug target for the treatment of fungal infections. The discovery of new efficient fungal CYP51 inhibitors requires an understanding of the structural requirements for selectivity for the fungal over the human ortholog. In this study, a binding mode of the pyridylethanol(phenylethyl)amine type CYP51 inhibitor to the human ortholog was determined at the atomic level. We isolated and purified a full-length human CYP51. The inhibitor-specific binding and its conformational and dynamic properties were evaluated using UV–visible and NMR spectroscopy.

Molecular Mechanism of the Inhibition and Remodeling of Human Islet Amyloid Polypeptide (hIAPP1–37) Oligomer by Resveratrol from Molecular Dynamics Simulation

Qianqian Wang, Lulu Ning, Yuzhen Niu, Huanxiang Liu [Lanzhou University], Xiaojun Yao

J. Phys. Chem. B., **119**, 15–24, 2015.

Natural polyphenols are one of the most actively investigated categories of amyloid inhibitors, and resveratrol has recently been reported to inhibit and remodel the human islet amyloid polypeptide (hIAPP) oligomers and fibrils. However, the exact mechanism of its action is still unknown, especially for the full-length hIAPP1–37. To this end, we performed all-atom molecular dynamics simulations for hIAPP1–37 pentamer with and without resveratrol. The obtained results show that the binding of resveratrol is able to cause remarkable conformational changes of hIAPP1–37 pentamer, in terms of secondary structures, order degree, and morphology.

Enzyme Catalysis

Role of the Active Site Guanine in the glmS Ribozyme Self-Cleavage Mechanism: Quantum Mechanical/Molecular Mechanical Free Energy Simulations

Sixue Zhang, Abir Ganguly, Puja Goyal, Jamie L. Bingaman, Philip C. Bevilacqua, Sharon Hammes-Schiffer [University of Illinois at Urbana—Champaign]

J. Am. Chem. Soc., **137**, 784–798, 2015.

The glmS ribozyme catalyzes a self-cleavage reaction at the phosphodiester bond between residues A-1 and G1. This reaction is thought to occur by an acid–base mechanism involving the glucosamine-6-phosphate cofactor and G40 residue. Herein quantum mechanical/molecular mechanical free energy simulations and pKa calculations, as well as experimental measurements of the rate constant for self-cleavage, are utilized to elucidate the mechanism, particularly the role of G40. Our calculations suggest that an external base deprotonates either G40(N1) or possibly A-1(O2'), which would be followed by proton transfer from G40(N1) to A-1(O2').

Enzyme Catalysis (Cont'd)

Theoretical study of the mechanism of protein arginine deiminase 4 (PAD4) inhibition by F-amidine

Dongmei Li [Nankai University], Cui Liu, Jianping Lin

J. Mol.Graph. and Mod., 55,25-32,2015.

Protein arginine deiminase 4 (PAD4) catalyzes the hydrolysis of a peptidylarginine residue to form a citrulline residue and ammonia during posttranslational modification. This process plays a pivotal role in rheumatoid arthritis (RA) and gene regulation. F-amidine belongs to a series of haloacetamide compounds that are the most potent PAD4 inhibitors described to date. F-amidine acts as a mechanism-based inhibitor of PAD4, inactivating PAD4 by the covalent modification of the active site Cys645. In this manuscript, the fundamental mechanism of PAD4 inhibition by F-amidine is investigated using a QM/MM approach.

A DFT study of the unusual substrate-assisted mechanism of *Serratia marcescens* chitinase B reveals the role of solvent and mutational effect on catalysis

Jitrayut Jitonnorn [University of Phayao], Chanchai Sattayanon, Nawee Kungwan, Supa Hannongbua

J. Mol.Graph. and Mod., 56, 53-59,2015.

Serratia marcescens chitinase B (SmChiB) catalyzes the hydrolysis of β -1,4-glycosidic bond, via an unusual substrate-assisted mechanism, in which the substrate itself acts as an intramolecular nucleophile. In this paper, the catalytic mechanism of SmChiB has been investigated by using density functional theory. The details of two consecutive steps (glycosylation and deglycosylation), the structures and energetics along the whole catalytic reaction, and the roles of solvent molecules as well as some conserved SmChiB residues (Asp142, Tyr214, Asp215, and Arg294) during catalysis are highlighted. Our calculations show that the formation of the oxazolinium cation intermediate in the glycosylation step was found to be a rate-determining step (with a barrier of 23 kcal/mol), in line with our previous computational studies.

Theoretical studies of the nitrogen containing compounds adsorption behavior on Na(I)Y and rare earth exchanged RE(III)Y zeolites

Wei Geng, Haitao Zhang, Xuefei Zhao, Wenyan Zan, Xionghou Gao, Xiaojun Yao [Lanzhou University]

J. Mol.Mod., 21, 10, 2015.

Protein phosphatase-5 (PP5), a novel target for inhibition in a search for new antitumor drugs, contains a homobimetallic $Mn^{II}Mn^{II}$ system in its catalytic site. The ground electronic state is an antiferromagnetically-coupled singlet. We report optimizations of a known inhibitor within a 42-residue model of the PP5 catalytic site under several two-level hybrid ONIOM computational models. Using the high-resolution crystal structure of a PP5/inhibitor complex as reference, we compare geometric parameters as the qualities of the "high-level" and "low-level" wavefunctions are successively improved by using the correct antiferromagnetic (AF) singlet state.

Enzyme Catalysis (Cont'd)

Multiple proton relay routes in the reaction mechanism of RNAP II: Assessing the effect of structural model

Rui Zhang, Anirban Bhattacharjee, Martin J. Field , Dennis R. Salahub[University of Calgary]

Proteins: Stru. Fun. & Bioinf., **83**, 268–281, 2015.

RNA polymerase II catalyzes the nucleotidyl transfer reaction for messenger RNA synthesis in eukaryotes. Two crystal structures of this system have been resolved, each with its own defects in the coordination sphere of $Mg^{2+}(A)$ resulting from chemical modifications. We have used both structures and also a novel hybrid of the two that allows a better exploration of the parts of configuration space that reflect substrate–enzyme interactions. MD and QM/MM calculations have been performed, the latter with the semiempirical AM1/d-PhoT method, calibrated against density functional theory. Reaction path scans in 1-D provided insights about the role of $Mg^{2+}(A)$ which turns out to be more structural than catalytic.

Computing the Role of Near Attack Conformations in an Enzyme-Catalyzed Nucleophilic Bimolecular Reaction

S. Kashif Sadiq , Peter V. Coveney [University College London]

J. Chem. Theor. and Comp., **11**, 316–324, 2015.

Near attack conformations (NACs) are conformations extending from the ground state (GS) that lie on the transition path of a chemical reaction. Here, we develop a method for computing the thermodynamic contribution to catalysis due to NAC formation in bimolecular reactions, within the limit of a classical molecular dynamics force field. We make use of the Bürgi–Dunitz theory applied to large-scale unbiased all-atom ensemble molecular dynamics simulations. We apply this to HIV-1 protease peptide hydrolysis, known to achieve a rate enhancement of $\sim 10^{11}$ ($\Delta G_{cat}^\ddagger \sim 15$ kcal/mol) over the uncatalyzed bimolecular reaction ($\Delta G_{non}^\ddagger \sim 30$ kcal/mol).

Chemical and protein structural basis for biological crosstalk between PPAR α and COX enzymes

Ann E. Cleves, Ajay N. Jain [University of California]

J.Comp.Aided. Mol.des. **29**, 101-112, 2015.

We have previously validated a probabilistic framework that combined computational approaches for predicting the biological activities of small molecule drugs. Molecule comparison methods included molecular structural similarity metrics and similarity computed from lexical analysis of text in drug package inserts. Here we present an analysis of novel drug/target predictions, focusing on those that were not obvious based on known pharmacological crosstalk. Considering those cases where the predicted target was an enzyme with known 3D structure allowed incorporation of information from molecular docking and protein binding pocket similarity in addition to ligand-based comparisons.

Enzyme Catalysis (Cont'd)

Combined computational and experimental analysis of a complex of ribonuclease III and the regulatory macrodomain protein, YmdB

Samridhdi Paudyal, Mercedes Alfonso-Prieto, Vincenzo Carnevale, Shiv K. Redhu, Michael L. Klein, Allen W. Nicholson[Temple University]

Proteins: Stru. Fun. & Bioinf., **83**, 459–472, 2015.

Ribonuclease III is a conserved bacterial endonuclease that cleaves double-stranded(ds) structures in diverse coding and noncoding RNAs. RNase III is subject to multiple levels of control that in turn confer global post-transcriptional regulation. The *Escherichia coli* macrodomain protein YmdB directly interacts with RNase III, and an increase in YmdB amount in vivo correlates with a reduction in RNase III activity. Here, a computational-based structural analysis was performed to identify atomic-level features of the YmdB-RNase III interaction.

High-Level QM/MM Calculations Support the Concerted Mechanism for Michael Addition and Covalent Complex Formation in Thymidylate Synthase

Nopporn Kaiyawet, Richard Lonsdale, Thanyada Rungrotmongkol, Adrian J. Mulholland, Supot Hannongbua [Chulalongkorn University]

J. Chem. Theor. and Comp., **11**, 713–722, 2015.

Thymidylate synthase (TS) is a promising cancer target, due to its crucial function in thymine synthesis. It performs the reductive methylation of 2'-deoxyuridine-5'-phosphate (dUMP) to thymidine-5'-phosphate (dTMP), using N-5,10-methylene-5,6,7,8-tetrahydrofolate (mTHF) as a cofactor. After the formation of the dUMP/mTHF/TS noncovalent complex, and subsequent conformational activation, this complex has been proposed to react via nucleophilic attack (Michael addition) by Cys146, followed by methylene-bridge formation to generate the ternary covalent intermediate. Herein, QM/MM (B3LYP-D/6-31+G(d)-CHARMM27) methods are used to model the formation of the ternary covalent intermediate. A two-dimensional potential energy surface reveals that the methylene-bridged intermediate is formed via a concerted mechanism, as indicated by a single transition state on the minimum energy pathway and the absence of a stable enolate intermediate.

Computational Rationale for the Selective Inhibition of the Herpes Simplex Virus Type 1 Uracil-DNA Glycosylase Enzyme

Umraan Hendricks, Werner Crous, Kevin J. Naidoo [University of Cape Town]

J.Chem. Infor. and Mod. **54**, 3362–3372, 2014.

The herpes simplex virus uracil-DNA glycosylase (hsvUNG) enzyme is responsible for the reactivation of the virus from latency and efficient viral replication in nerve tissue. The lack of uracil-DNA glycosylase enzyme in human neurons and the continuous deamination of cytosine create an environment where the presence of viral uracil-DNA glycosylase is a necessity for the proliferation of the virus. Here, by using a combination of sequence and structural comparisons between the two enzymes along with free energy of binding computations and principal component analysis of the ligands, we investigate and rationalize the inhibitory effect of the 6-(4-alkylanilino)-uracil series as a function of alkyl chain length on the hsvUNG.

Enzyme Catalysis (Cont'd)

Conformational diversity of bacterial FabH: Implications for molecular recognition specificity

Pages Anuradha Mittal, Michael E. Johnson [University of Illinois at Chicago]

J. Mol. Graph. and Mod., **55**, 115-122, 2015.

The molecular basis of variable substrate and inhibitor specificity of the highly conserved bacterial fatty acid synthase enzyme, FabH, across different bacterial species remains poorly understood. In the current work, we explored the conformational diversity of FabH enzymes to understand the determinants of diverse interaction specificity across Gram-positive and Gram-negative bacteria. Atomistic molecular dynamics simulations reveal that FabH from *E. coli* and *E. faecalis* exhibit distinct native state conformational ensembles and dynamic behaviors.

Mechanism-Based Discovery of Novel Substrates of Haloalkane Dehalogenases Using in Silico Screening

Lukas Daniel, Tomas Buryska, Zbynek Prokop, Jiri Damborsky, Jan Brezovsky [Masaryk University]

J. Chem. Infor. and Mod. **55**, 54–62, 2015.

Substrate specificity is a key feature of enzymes determining their applicability in biomaterials and biotechnologies. Experimental testing of activities with novel substrates is a time-consuming and inefficient process, typically resulting in many failures. Here, we present an experimentally validated in silico method for the discovery of novel substrates of enzymes with a known reaction mechanism. The method was developed for a model system of biotechnologically relevant enzymes, haloalkane dehalogenases. On the basis of the parametrization of six different haloalkane dehalogenases with 30 halogenated substrates, mechanism-based geometric criteria for reactivity approximation were defined.

Understanding the Thermostability and Activity of *Bacillus subtilis* Lipase Mutants: Insights from Molecular Dynamics Simulations

Bipin Singh, Gopalakrishnan Bulusu, Abhijit Mitra [International Institute of Information Technology Hyderabad (IIIT-H)]

J. Phys. Chem. B., **119**, 392–409, 2015.

Improving the thermostability of industrial enzymes is an important protein engineering challenge. Point mutations, induced to increase thermostability, affect the structure and dynamics of the target protein in several ways and thus can also affect its activity. There appears to be no general rules for improving the thermostability of enzymes without adversely affecting their enzymatic activity. We report MD simulations, of wild type *Bacillus subtilis* lipase (WT) and its six progressively thermostable mutants (2M, 3M, 4M, 6M, 9M, and 12M), performed at different temperatures, to address this issue.

Enzyme Catalysis (Cont'd)

Free Energy Simulations of Active-Site Mutants of Dihydrofolate Reductase

Dvir Doron, Vanja Stojković, Lokesh Gakhar, Alexandra Vardi-Kilshtain, Amnon Kohen, Dan Thomas Major [Bar-Ilan University]

J. Phys. Chem. B., **119**, 906–916, 2015.

This study employs hybrid quantum mechanics–molecular mechanics (QM/MM) simulations to investigate the effect of mutations of the active-site residue I14 of *E. coli* dihydrofolate reductase (DHFR) on the hydride transfer. Recent kinetic measurements of the I14X mutants (X = V, A, and G) indicated slower hydride transfer rates and increasingly temperature-dependent kinetic isotope effects (KIEs) with systematic reduction of the I14 side chain. The QM/MM simulations show that when the original isoleucine residue is substituted in silico by valine, alanine, or glycine (I14V, I14A, and I14G DHFR, respectively), the free energy barrier height of the hydride transfer reaction increases relative to the wild-type enzyme.

Enzymatic Minimum Free Energy Path Calculations Using Swarms of Trajectories

Melchor Sanchez-Martinez, Martin Field, Ramon Crehuet Institute of Advanced Chemistry of Catalonia (IQAC)]

J. Phys. Chem. B., **119**, 1103–1113, 2015.

The development of approaches for simulating rare events in complex molecular systems is a central concern in chemical physics. In recent work, Roux and co-workers proposed a novel, swarms of trajectories (SoT) method for determining the transition paths of such events. It consists of the dynamical refinement on the system's free energy surface of a putative transition path that is parametrized in terms of a set of collective variables (CVs) that are identified as being important for the transition. In this work, we have implemented the SoT method and used it to investigate the catalytic mechanisms of two enzymatic reactions using hybrid QM/MM potentials.

Enzyme Promiscuity in Enolase Superfamily. Theoretical Study of *o*-Succinylbenzoate Synthase Using QM/MM Methods

María Sánchez-Tarín, Katarzyna Swiderek, Maite Roca [Lodz University of Technology], Iñaki Tuñón

J. Phys. Chem. B., **119**, 1899–1911, 2015.

The promiscuous activity of the enzyme *o*-succinylbenzoate synthase (OSBS) from the actinobacteria *Ammycolatopsis* is investigated by means of QM/MM methods, using both density functional theory and semiempirical Hamiltonians. This enzyme catalyzes not only the dehydration of 2-succinyl-6R-hydroxy-2,4-cyclohexadiene-1R-carboxylate but also catalyzes racemization of different acylamino acids, with *N*-succinyl-R-phenylglycine being the best substrate. We investigated the molecular mechanisms for both reactions exploring the potential energy surface. Then, molecular dynamics simulations were performed to obtain the free energy profiles and the averaged interaction energies of enzymatic residues with the reacting system.

Protein-Protein Interactions

CCharPPI web server: computational characterization of protein–protein interactions from structure

Iain H. Moal, Brian Jiménez-García, Juan Fernández-Recio[Barcelona Supercomputing Center]

Bioinformatics. **30**, 123–125, 2015.

The atomic structures of protein–protein interactions are central to understanding their role in biological systems, and a wide variety of biophysical functions and potentials have been developed for their characterization and the construction of predictive models. These tools are scattered across a multitude of stand-alone programs, and are often available only as model parameters requiring reimplementations. This acts as a significant barrier to their widespread adoption. CCharPPI integrates many of these tools into a single web server.

Non-interacting surface solvation and dynamics in protein–protein interactions

Koen M. Visscher, Panagiotis L. Kastitis and Alexandre M. J. J. Bonvin[Utrecht University]

Proteins: Stru. Fun. & Bioinf., **83**, 445–458, 2015.

Protein–protein interactions control a plethora of cellular processes, including cell proliferation, differentiation, apoptosis, and signal transduction. Understanding how and why proteins interact will inevitably lead to novel structure-based drug design methods, as well as design of de novo binders with preferred interaction properties. At a structural and molecular level, interface and rim regions are not enough to fully account for the energetics of protein–protein binding, even for simple lock-and-key rigid binders. As we have recently shown, properties of the global surface might also play a role in protein–protein interactions.

Membrane Proteins and Lipid Peptide Interactions

Coupled Diffusion in Lipid Bilayers upon Close Approach

Sander Pronk, Erik Lindahl, Peter M. Kasson[University of Virginia]

J. Am. Chem. Soc., **137**, 708–714, 2015.

Biomembrane interfaces create regions of slowed water dynamics in their vicinity. When two lipid bilayers come together, this effect is further accentuated, and the associated slowdown can affect the dynamics of larger-scale processes such as membrane fusion. We have used molecular dynamics simulations to examine how lipid and water dynamics are affected as two lipid bilayers approach each other. These two interacting fluid systems, lipid and water, both slow and become coupled when the lipid membranes are separated by a thin water layer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Long-timescale motions in glycerol-monopalmitate lipid bilayers investigated using molecular dynamics simulation

Monika Laner [Laboratory of Physical Chemistry, ETH Zürich], Bruno A.C. Horta, Philippe H. Hünenberger

J. Mol.Graph. and Mod., **55**, 48-64,2015.

The occurrence of long-timescale motions in glycerol-1-monopalmitate (GMP) lipid bilayers is investigated based on previously reported 600 ns molecular dynamics simulations of a $2 \times 8 \times 8$ GMP bilayer patch in the temperature range 302–338 K, performed at three different hydration levels, or in the presence of the cosolutes methanol or trehalose at three different concentrations. The types of long-timescale motions considered are: (i) the possible phase transitions; (ii) the precession of the relative collective tilt-angle of the two leaflets in the gel phase; (iii) the trans–gauche isomerization of the dihedral angles within the lipid aliphatic tails; and (iv) the flipping of single lipids across the two leaflets.

Effect of methanol on the phase-transition properties of glycerol-monopalmitate lipid bilayers investigated using molecular dynamics simulations: In quest of the biphasic effect

Monika Laner, Philippe H. Hünenberger [Laboratory of Physical Chemistry, ETH Zürich]

J. Mol.Graph. and Mod., **55**, 85-104,2015.

The effect of methanol on the phase and phase-transition properties of a $2 \times 8 \times 8$ glycerol-1-monopalmitate bilayer patch is investigated using a series of 239 molecular dynamics simulations on the 180 ns timescale, considering methanol concentrations cM and temperatures T in the ranges 0–12.3 M and 302–338 K, respectively. The results in the form of hysteresis-corrected transition temperatures T_m are compatible with the expected features of the biphasic effect, with a reversal concentration c_{rev} of about 5.2 M. Below this concentration, the main transition is between the liquid crystal (LC) and gel (GL) phases, and T_m decreases upon increasing cM.

Dry Martini, a Coarse-Grained Force Field for Lipid Membrane Simulations with Implicit Solvent

Clément Arnarez, Jaakko J. Uusitalo, Marcelo F. Masman, Helgi I. Ingólfsson, Djurre H. de Jong, Manuel N. Melo, Xavier Periole, Alex H. de Vries, and Siewert J. Marrink [University of Groningen]

J. Chem. Theor. and Comp., **11**, 260–275, 2015.

Coarse-grained (CG) models allow simulation of larger systems for longer times by decreasing the number of degrees of freedom compared with all-atom models. Here we introduce an implicit-solvent version of the popular CG Martini model, nicknamed “Dry” Martini. To account for the omitted solvent degrees of freedom, the nonbonded interaction matrix underlying the Martini force field was reparametrized. The Dry Martini force field reproduces relatively well a variety of lipid membrane properties such as area per lipid, bilayer thickness, bending modulus, and coexistence of liquid-ordered and disordered domains.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Identification of Protein–Ligand Binding Sites by the Level-Set Variational Implicit-Solvent Approach

Zuojun Guo, Bo Li, Li-Tien Cheng, Shenggao Zhou, J. Andrew McCammon, Jianwei Che [Genomics Institute of the Novartis Research Foundation]

J. Chem. Theor. and Comp., **11**, 753–765, 2015.

Protein–ligand binding is a key biological process at the molecular level. The identification and characterization of small-molecule binding sites on therapeutically relevant proteins have tremendous implications for target evaluation and rational drug design. In this work, we used the recently developed level-set variational implicit-solvent model (VISM) with the Coulomb field approximation (CFA) to locate and characterize potential protein–small-molecule binding sites. We applied our method to a data set of 515 protein–ligand complexes and found that 96.9% of the cocrystallized ligands bind to the VISM-CFA-identified pockets and that 71.8% of the identified pockets are occupied by cocrystallized ligands.

Binding energy calculations for hevein–carbohydrate interactions using expanded ensemble molecular dynamics simulations

Chaitanya A. K. Koppisetty, Martin Frank, Alexander P. Lyubartsev, Per-Georg Nyholm [University of Gothenburg]

J. Comp. Aided. Mol. des., **29**, 13-21, 2015.

Accurate estimation of protein–carbohydrate binding energies using computational methods is a challenging task. Here we report the use of expanded ensemble molecular dynamics (EEMD) simulation with double decoupling for estimation of binding energies of hevein, a plant lectin with its monosaccharide and disaccharide ligands GlcNAc and (GlcNAc)₂, respectively. In addition to the binding energies, enthalpy and entropy components of the binding energy are also calculated. The estimated binding energies for the hevein–carbohydrate interactions are within the range of ± 0.5 kcal of the previously reported experimental binding data.

Discovery of Multitarget-Directed Ligands against Alzheimer’s Disease through Systematic Prediction of Chemical–Protein Interactions

Jiansong Fang, Yongjie Li, Rui Liu, Xiaocong Pang, Chao Li, Ranyao Yang, Yangyang He, Wenwen Lian, Ai-Lin Liu [Chinese Academy of Medical Sciences and Peking Union Medical College], Guan-Hua Du

J. Chem. Infor. and Mod., **55**, 149–164, 2015.

To determine chemical–protein interactions (CPI) is costly, time-consuming, and labor-intensive. In silico prediction of CPI can facilitate the target identification and drug discovery. Although many in silico target prediction tools have been developed, few of them could predict active molecules against multitarget for a single disease. In this investigation, naive Bayesian (NB) and recursive partitioning (RP) algorithms were applied to construct classifiers for predicting the active molecules against 25 key targets toward Alzheimer’s disease (AD) using the multitarget-quantitative structure–activity relationships (mt-QSAR) method. Each molecule was initially represented with two kinds of fingerprint descriptors (ECFP6 and MACCS).

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Electroporation Threshold of POPC Lipid Bilayers with Incorporated Polyoxyethylene Glycol (C12E8)

Andraž Polak, Aljaž Velikonja, Peter Kramar, Mounir Tarek, Damijan Miklavčič [University of Ljubljana]

J. Phys. Chem. B., **119**, 192–200, 2015.

Electroporation relates to a phenomenon in which cell membranes are permeabilized after being exposed to high electric fields. On the molecular level, the mechanism is not yet fully elucidated, although a considerable body of experiments and MD simulations were performed on model membranes. Here we present the results of a combined theoretical and experimental investigation of electroporation of palmitoyl-oleoyl-phosphatidylcholine (POPC) bilayers with incorporated polyoxyethylene glycol (C12E8) surfactants. The experimental results show a slight increase of the capacitance and a 22% decrease of the voltage breakdown upon addition of C12E8 to pure POPC bilayers.

Interactions of Lipids and Detergents with a Viral Ion Channel Protein: Molecular Dynamics Simulation Studies

Sarah L. Rouse, Mark S. P. Sansom [University of Oxford]

J. Phys. Chem. B., **119**, 764–772, 2015.

Structural studies of membrane proteins have highlighted the likely influence of membrane mimetic environments (i.e., lipid bilayers versus detergent micelles) on the conformation and dynamics of small α -helical membrane proteins. We have used molecular dynamics simulations to compare the conformational dynamics of BM2 (a small α -helical protein from the membrane of influenza B) in a model phospholipid bilayer environment with its behavior in protein-detergent complexes with either the zwitterionic detergent dihexanoylphosphatidylcholine (DHPC) or the nonionic detergent dodecylmaltoside (DDM).

Combined Quantum Mechanics/Molecular Mechanics (QM/MM) Simulations for Protein–Ligand Complexes: Free Energies of Binding of Water Molecules in Influenza Neuraminidase

Christopher J. Woods, Katherine E. Shaw, Adrian J. Mulholland [University of Bristol]

J. Phys. Chem. B., **119**, 997–1001, 2015.

The applicability of combined quantum mechanics/molecular mechanics (QM/MM) methods for the calculation of absolute binding free energies of conserved water molecules in protein/ligand complexes is demonstrated. Here, we apply QM/MM Monte Carlo simulations to investigate binding of water molecules to influenza neuraminidase. We investigate five different complexes, including those with the drugs oseltamivir and peramivir. We investigate water molecules in two different environments, one more hydrophobic and one hydrophilic. We calculate the free-energy change for perturbation of a QM to MM representation of the bound water molecule.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Structures of Fluid Phosphatidylethanolamine Bilayers Obtained from Simulation-to-Experiment Comparisons and Experimental Scattering Density Profiles

Norbert Kučerka, Brad van Oosten, Jianjun Pan, Frederick A. Heberle, Thad A. Harroun, John Katsaras [University of Tennessee]

J. Phys. Chem. B., **119**, 1947–1956, 2015.

Following our previous efforts in determining the structures of commonly used PC, PG, and PS bilayers, we continue our studies of fully hydrated, fluid phase PE bilayers. The newly designed parsing scheme for PE bilayers was based on extensive MD simulations, and is utilized in the SDP analysis of both X-ray and neutron (contrast varied) scattering measurements. Obtained experimental scattering form factors are directly compared to our simulation results, and can serve as a benchmark for future developed force fields. Among the evaluated structural parameters, namely, area per lipid A, overall bilayer thickness DB, and hydrocarbon region thickness 2DC, the PE bilayer response to changing temperature is similar to previously studied bilayers with different headgroups.

Protein-Nucleic acid Interactions

Designing Peptide Sequences in Flexible Chain Conformations to Bind RNA: A Search Algorithm Combining Monte Carlo, Self-Consistent Mean Field and Concerted Rotation Techniques

Xingqing Xiao, Paul F. Agris, Carol K. Hall [North Carolina State University]

J. Chem. Theor. and Comp., **11**, 740–752, 2015.

A search algorithm combining Monte Carlo, self-consistent mean field, and concerted rotation techniques was developed to discover peptide sequences that are reasonable HIV drug candidates due to their exceptional binding to human tRNA^{UUU}Lys3, the primer of HIV replication. The search algorithm allows for iteration between sequence mutations and conformation changes during sequence evolution. Searches conducted for different classes of peptides identified several potential peptide candidates. Analysis of the energy revealed that the asparagine and cysteine at residues 11 and 12 play important roles in “recognizing” tRNA^{Lys3} via van der Waals interactions, contributing to binding specificity.

Free-Energy Calculations Reveal the Subtle Differences in the Interactions of DNA Bases with α -Hemolysin

Richard M. A. Manara, Andrew T. Guy, E. Jayne Wallace, Syma Khalid [University of Southampton]

J. Chem. Theor. and Comp., **11**, 810–816, 2015.

Next generation DNA sequencing methods that utilize protein nanopores have the potential to revolutionize this area of biotechnology. While the technique is underpinned by simple physics, the wild-type protein pores do not have all of the desired properties for efficient and accurate DNA sequencing. Much of the research efforts have focused on protein nanopores, such as α -hemolysin from *Staphylococcus aureus*. However, the speed of DNA translocation has historically been an issue, hampered in part by incomplete knowledge of the energetics of translocation.

Protein-Nucleic acid Interactions (Cont'd)

Ligand 5,10,15,20-Tetra(N-methyl-4-pyridyl)porphine (TMPyP4) Prefers the Parallel Propeller-Type Human Telomeric G-Quadruplex DNA over Its Other Polymorphs

Asfa Ali, Manju Bansal, Santanu Bhattacharya [Jawaharlal Nehru Centre for Advanced Scientific Research]

J. Phys. Chem. B., **119**, 5–14, 2015.

The binding of ligand 5,10,15,20-tetra(N-methyl-4-pyridyl)porphine (TMPyP4) with telomeric and genomic G-quadruplex DNA has been extensively studied. However, a comparative study of interactions of TMPyP4 with different conformations of human telomeric G-quadruplex DNA, namely, parallel propeller-type (PP), antiparallel basket-type (AB), and mixed hybrid-type (MH) G-quadruplex DNA, has not been done. We considered all the possible binding sites in each of the G-quadruplex DNA structures and docked TMPyP4 to each one of them. The resultant most potent sites for binding were analyzed from the mean binding free energy of the complexes.

Interaction of Palmatine with DNA: An Environmentally Controlled Phototherapy Drug

Élise Dumont , Antonio Monari [Université de Lorraine Nancy]

J. Phys. Chem. B., **119**, 410–419, 2015.

Palmatine is one of the four main protoberberine alkaloids and is largely employed in pharmacy and medicine as a versatile drug with considerable biological activities. More recently, palmatine has been proposed as a promising DNA phototherapy drug, notably due to its ability to produce in situ singlet oxygen only when interacting with DNA. The fine mechanisms of palmatine—DNA interactions as well as its complicated photophysics are not yet fully understood. In this paper, we identify via molecular dynamic techniques two stable interaction modes between palmatine and B-DNA, namely insertion and minor groove binding, whose structural and electronic bases are analyzed and rationalized.

Binding Site Preorganization and Ligand Discrimination in the Purine Riboswitch

Johan Sund, Christoffer Lind, Johan Åqvist [Uppsala University]

J. Phys. Chem. B., **119**, 773–782, 2015.

The progress of RNA research has suggested a wide variety of RNA molecules as possible targets for pharmaceutical drug molecules. Structure-based computational methods for predicting binding modes and affinities are now important tools in drug discovery, but these methods have mainly been focused on protein targets. Here we employ molecular dynamics free-energy perturbation calculations and the linear interaction energy method to analyze the energetics of ligand binding to purine riboswitches.

Nucleic Acids

Multiscale Simulations of Human Telomeric G-Quadruplex DNA

Matúš Rebič, Francesca Mocci, Aatto Laaksonen, Jozef Uličný [P. J. Šafárik University]

J. Phys. Chem. B., **119**, 105–113, 2015.

We present a coarse-grain (CG) model of human telomeric G-quadruplex, obtained using the inverse Monte Carlo (IMC) and iterative Boltzmann inversion (IBI) techniques implemented within the software package called MagiC. As a starting point, the 2HY9 human telomeric [3 + 1] hybrid, a 26-nucleobase sequence, was modeled performing a 1 μ s long atomistic molecular dynamics (MD) simulation. The chosen quadruplex includes two kinds of loops and all possible combinations of relative orientations of guanine strands that can be found in quadruplexes.

Coarse-Grained Simulation Study of Sequence Effects on DNA Hybridization in a Concentrated Environment

Cade B. Markegard, Iris W. Fu, K. Anki Reddy, Hung D. Nguyen [University of California—Irvine]

J. Phys. Chem. B., **119**, 1823–1834, 2015.

A novel coarse-grained model is developed to elucidate thermodynamics and kinetic mechanisms of DNA self-assembly. It accounts for sequence and solvent conditions to capture key experimental results such as sequence-dependent thermal property and salt-dependent persistence length of ssDNA and dsDNA. Moreover, constant-temperature simulations on two single strands of a homogeneous sequence show two main mechanisms of hybridization: a slow slithering mechanism and a one-order faster zippering mechanism. This study yields a complex picture on the role of sequence on programmable self-assembly and demonstrates a promising simulation tool that is suitable for studies in DNA nanotechnology.

Loop Contributions to the Folding Thermodynamics of DNA Straight Hairpin Loops and Pseudoknots

Calliste Reiling, Irine Khutsishvili, Kai Huang, Luis A. Marky [University of Nebraska Medical Center]

J. Phys. Chem. B., **119**, 1939–1946, 2015.

Pseudoknots have diverse and important roles in many biological functions. We used a combination of UV spectroscopy and differential scanning calorimetry to investigate the effect of the loop length on the unfolding thermodynamics of three sets of DNA stem-loop motifs with the following sequences: (a) d(GCGCTnGCGC), where $n = 3, 5, 7, 9$; (b) d(CGCGCGT4GAAATTCGCGCGTnAATTTC), where $n = 4, 6$, and 8 ; and (c) d(TCTCTnAAAAAAAAAGAGAT5TTTTTTT), where $n = 5, 7, 9$, and 11 . The increase in loop length of the first set of hairpins yielded decreasing T_M 's and constant unfolding enthalpies, resulting in an entropy driven decrease in the stability of the hairpin ($\Delta G^\circ = -7.5$ to -6.1 kcal/mol).

Surfaces, Catalysts, and Materials Subjects

Computational study of elements of stability of a four-helix bundle protein biosurfactant

Andrea Schaller, Natalie K. Connors [The University of Queensland], Mirjana Dimitrijevic Dwyer, Stefan A. Oelmeier, Jürgen Hubbuch, Anton P. J. Middelberg

J.Comp.Aided. Mol.des. **29**, 47-58, 2015.

A MD simulation protocol was developed to model halogen bonding in protein–ligand complexes by inclusion of a charged extra point to represent the anisotropic distribution of charge on the halogen atom. This protocol was then used to simulate the interactions of cathepsin L with a series of halogenated and non-halogenated inhibitors. Our results show that chloro, bromo and iodo derivatives have progressively narrower distributions of calculated geometries, which reflects the order of affinity $I > Br > Cl$, in agreement with the IC_{50} values. Graphs for the Cl, Br and I analogs show stable interactions between the halogen atom and the Gly61 carbonyl oxygen of the enzyme.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Visually impaired researchers get their hands on quantum chemistry: application to a computational study on the isomerization of a sterol

Valère Lounnas, Henry B. Wedler [University of California – Davis], Timothy Newman, Gijs Schaftenaar, Jason G. Harrison, Gabriella Nepomuceno, Ryan Pemberton, Dean J. Tantillo, Gert Vriend

J.Comp.Aided. Mol.des. **29**, 1057-1067, 2015.

3-D ligand conformations are required for most ligand-based drug design methods, such as pharmacophore modeling, shape-based screening, and 3-D QSAR model building. Many studies of conformational search methods have focused on the reproduction of crystal structures (i.e. bioactive conformations); however, for ligand-based modeling the key question is how to generate a ligand alignment that produces the best results for a given query molecule. In this work, we study different conformation generation modes of ConfGen and the impact on virtual screening (Shape Screening and e-Pharmacophore) and QSAR predictions (atom-based and field-based).

How Experimental Errors Influence Drug Metabolism and Pharmacokinetic QSAR/QSPR Models

Mark C. Wenlock [AstraZeneca R&D Mölndal], Lars A. Carlsson

J.Chem. Infor. and Mod. **55**, 125–134, 2015.

We consider the impact of gross, systematic, and random experimental errors in relation to their impact on the predictive ability of QSAR/QSPR DMPK models used within early drug discovery. Models whose training sets contain fewer but repeatedly measured data points, with a defined threshold for the random error, resulted in prediction improvements ranging from 3.3% to 23.0% for an external test set, compared to models built from training sets in which the molecules were defined by single measurements.

Potentials and Parameters

Local Perturbation Analysis: A Computational Tool for Biophysical Reaction-Diffusion Models

William R. Holmes [University of Melbourne], May Anne Mata, Leah Edelstein-Keshet

Biophysical Journal. **108**, 230-236, 2015.

Diffusion and interaction of molecular regulators in cells is often modeled using reaction-diffusion partial differential equations. Analysis of such models and exploration of their parameter space is challenging, particularly for systems of high dimensionality. Here, we present a relatively simple and straightforward analysis, the local perturbation analysis, that reveals how parameter variations affect model behavior. This computational tool, which greatly aids exploration of the behavior of a model, exploits a structural feature common to many cellular regulatory systems: regulators are typically either bound to a membrane or freely diffusing.

Using support vector machines to identify protein phosphorylation sites in viruses

Shu-Yun Huang, Shao-Ping Shi, Jian-Ding Qiu [Nanchang University], Ming-Chu Liu

J. Mol. Graph. and Mod., **56**, 84-90, 2015.

Phosphorylation of viral proteins plays important roles in enhancing replication and inhibition of normal host-cell functions. Given its importance in biology, a unique opportunity has arisen to identify viral protein phosphorylation sites. However, experimental methods for identifying phosphorylation sites are resource intensive. There is significant interest in developing computational methods for reliable prediction of viral phosphorylation sites from amino acid sequences. A new method based on support vector machine is proposed to identify protein phosphorylation sites in viruses.

Target-Specific Native/Decoy Pose Classifier Improves the Accuracy of Ligand Ranking in the CSAR 2013 Benchmark

Denis Fourches, Regina Politi, Alexander Tropsha [University of North Carolina at Chapel Hill]

J. Chem. Infor. and Mod. **55**, 63–71, 2015.

As part of the CSAR 2013 benchmark exercise, we have implemented a hybrid docking and scoring workflow to rank 10 steroid ligands of an engineered digoxigenin-binding protein. Schrödinger's Glide docking software was used to generate poses for each steroid ligand and rank them according to both standard docking precision (SP) and extra docking precision (XP) scoring functions. The unique component of our approach was the use of a target-specific pose classifier trained to discriminate natively-like from decoy poses. To build the classifier, a single cognate ligand with a known native pose (PDB code 4J8T) was docked multiple times into its target protein, and the generated poses were divided into two classes (natively-like and decoy) using a root-mean-square deviation threshold of 2 Å.

Residue-Specific Force Field Based on Protein Coil Library. RSFF2: Modification of AMBER ff99SB

Chen-Yang Zhou, Fan Jiang [Peking University Shenzhen Graduate School], Yun-Dong Wu

J. Phys. Chem. B., **119**, 1035–1047, 2015.

Recently, we developed a residue-specific force field (RSFF1) based on conformational free-energy distributions of the 20 amino acid residues from a protein coil library. Most parameters in RSFF1 were adopted from the OPLS-AA/L force field, but some van der Waals and torsional parameters that effectively affect local conformational preferences were introduced specifically for individual residues to fit the coil library distributions. Here a similar strategy has been applied to modify the Amber ff99SB force field, and a new force field named RSFF2 is developed.

Molecular Dynamics

Exact Stochastic Simulation of a Calcium Microdomain Reveals the Impact of Ca^{2+} Fluctuations on IP_3R Gating

Nicolas Wieder [Universität Heidelberg] , Rainer Fink, Frederic von Wegner

Biophysical Journal. **108**, 557-567, 2015.

In this study, we numerically analyzed the nonlinear Ca^{2+} -dependent gating dynamics of a single, nonconducting inositol 1,4,5-trisphosphate receptor (IP_3R) channel, using an exact and fully stochastic simulation algorithm that includes channel gating, Ca^{2+} buffering, and Ca^{2+} diffusion. The IP_3R is a ubiquitous intracellular Ca^{2+} release channel that plays an important role in the formation of complex spatiotemporal Ca^{2+} signals such as waves and oscillations. Dynamic subfemtoliter Ca^{2+} microdomains reveal low copy numbers of Ca^{2+} ions, buffer molecules, and IP_3Rs , and stochastic fluctuations arising from molecular interactions and diffusion do not average out.

Direct NMR Detection of Bifurcated Hydrogen Bonding in the α -Helix N-Caps of Ankyrin Repeat Proteins

Matthew R. Preimesberger, Ananya Majumdar, Tural Aksel, Kevin Sforza, Thomas Lectka, Doug Barrick, Juliette T. J. Lecomte [Johns Hopkins University]

J. Am. Chem. Soc., **137**, 1008–1011, 2015.

In biomolecules, bifurcated H-bonds typically involve the interaction of two donor protons with the two lone pairs of oxygen. Here, we present direct NMR evidence for a bifurcated H-bonding arrangement involving nitrogen as the acceptor atom. Specifically, the H-bond network comprises the N δ 1 atom of histidine and both the backbone N–H and side-chain O γ –H of threonine within the conserved TXXH motif of ankyrin repeat (AR) proteins. Identification of the H-bonding partners is achieved via solution NMR H-bond scalar coupling (HBC) and H/D isotope shift experiments.

Funnel-Metadynamics and Solution NMR to Estimate Protein–Ligand Affinities

Laura Troussicot, Florence Guillière, Vittorio Limongelli, Olivier Walker, Jean-Marc Lancelin [Université de Lyon]

J. Am. Chem. Soc., **137**, 1273–1281, 2015.

One of the intrinsic properties of proteins is their capacity to interact selectively with other molecules in their environment, inducing many chemical equilibria each differentiated by the mutual affinities of the components. A comprehensive understanding of these molecular binding processes at atomistic resolution requires formally the complete description of the system dynamics and statistics at the relevant time scales. While solution NMR observables are averaged over different time scales, from picosecond to second, recent new molecular dynamics protocols accelerated considerably the simulation time of realistic model systems.

BROMOC suite: Monte Carlo/Brownian dynamics suite for studies of ion permeation and DNA transport in biological and artificial pores with effective potentials

Pablo M. De Biase [University of Calgary], Suren Markosyan, Sergei Noskov

J. Comp. Chem., **36**, 264–271, 2015.

The transport of ions and solutes by biological pores is central for cellular processes and has a variety of applications in modern biotechnology. The time scale involved in the polymer transport across a nanopore is beyond the accessibility of conventional MD simulations. Moreover, experimental studies lack sufficient resolution to provide details on the molecular underpinning of the transport mechanisms. BROMOC, the code presented herein, performs Brownian dynamics simulations, both serial and parallel, up to several milliseconds long.

Molecular Dynamics (Cont'd)

Structure based computational assessment of channel properties of assembled ORF-8a from SARS-CoV

Hao-Jen Hsu, Meng-Han Lin, Christina Schindler , Wolfgang B. Fischer [National Yang-Ming University]

Proteins: Stru. Fun. & Bioinf., **83**, 300–308, 2015.

ORF 8a is a short 39 amino acid bitopic membrane protein encoded by severe acute respiratory syndrome causing corona virus (SARS-CoV). It has been identified to increase permeability of the lipid membrane for cations. Permeability is suggested to occur due to the assembly of helical bundles. Computational models of a pentameric assembly of 8a peptides are generated using the first 22 amino acids, which include the transmembrane domain. Low energy structures reveal a hydrophilic pore mantled by residues Thr-8, and -18, Ser-11, Cys-13, and Arg-22. Potential of mean force (PMF) profiles for mono (Na⁺, K⁺, Cl⁻) and divalent (Ca²⁺) ions along the pore are calculated.

Frequent side chain methyl carbon-oxygen hydrogen bonding in proteins revealed by computational and stereochemical analysis of neutron structures

Joseph D. Yesselman, Scott Horowitz, Charles L. Brooks III , Raymond C. Trievel[University of Michigan]

Proteins: Stru. Fun. & Bioinf., **83**, 403–410, 2015.

The propensity of backbone Ca atoms to engage in carbon-oxygen (CH•••O) hydrogen bonding is well-appreciated in protein structure, but side chain CH•••O hydrogen bonding remains largely uncharacterized. The extent to which side chain methyl groups in proteins participate in CH•••O hydrogen bonding is examined through a survey of neutron crystal structures, quantum chemistry calculations, and molecular dynamics simulations. Using these approaches, methyl groups were observed to form stabilizing CH•••O hydrogen bonds within protein structure that are maintained through protein dynamics and participate in correlated motion.

Parameterization of the DFTB3 Method for Br, Ca, Cl, F, I, K, and Na in Organic and Biological Systems

Maximilian Kubillus, Tomáš Kubař, Michael Gaus, Jan Řezáč, Marcus Elstner [Karlsruhe Institute of Technology]

J. Chem. Theor. and Comp., **11**, 332–342, 2015.

We present an extension to the recent 3OB parametrization of the Density Functional Tight Binding Model DFTB31,2 for biological and organic systems. Parameters for the halogens F, Cl, Br, and I have been developed for use in covalently bound systems and benchmarked on a test set of 106 molecules (the 'OrgX' set), using bonding distances, bonding angles, atomization energies, and vibrational frequencies to assess the performance of the parameters. Additional testing has been done with the X40 set of 40 supramolecular systems containing halogens,3 adding a simple correction for the halogen bonds that are strongly overbound in DFTB3.

Molecular dynamics simulation of halogen bonding mimics experimental data for cathepsin L inhibition

Cristian Celis-Barros, Leslie Saavedra-Rivas, J. Cristian Salgado, Bruce K. Cassels, Gerald Zapata-Torres[University of Chile]

J.Comp.Aided. Mol.des. **29**, 37-46, 2015.

A MD simulation protocol was developed to model halogen bonding in protein–ligand complexes by inclusion of a charged extra point to represent the anisotropic distribution of charge on the halogen atom. This protocol was used to simulate the cathepsin L with a series of halogenated and non-halogenated inhibitors. Results show that halo derivatives have progressively narrower distributions of calculated geometries, which reflects the order of affinity I > Br > Cl, in agreement with the IC₅₀ values. Graphs for the Cl, Br and I analogs show stable interactions between the halogen atom and the Gly61 carbonyl oxygen of the enzyme.

Molecular Dynamics (Cont'd)

Time-Averaged Distributions of Solute and Solvent Motions: Exploring Proton Wires of GFP and PfM2DH

Camilo Velez-Vega, Daniel J. J. McKay[Novartis Institutes for BioMedical Research], Vibhas Aravamuthan, Robert Pearlstein, José S. Duca

J.Chem. Infor. and Mod. **54**, 3344–3361, 2014.

Proton translocation pathways of selected variants of the green fluorescent protein (GFP) and *Pseudomonas fluorescens* mannitol 2-dehydrogenase (PfM2DH) were investigated via an explicit solvent molecular dynamics-based analysis protocol that allows for direct quantitative relationship between a crystal structure and its time-averaged solute–solvent structure obtained from simulation. Our study of GFP is in good agreement with previous research suggesting that the proton released from the chromophore upon photoexcitation can diffuse through an extended internal hydrogen bonding network that allows for the proton to exit to bulk or be recaptured by the anionic chromophore.

Effects of Water Concentration on the Free Volume of Amino Acid Ionic Liquids Investigated by Molecular Dynamics Simulations

Abdul Rajjak Shaikh, Eiji Kamio, Hiromitsu Takaba, Hideto Matsuyama [Kobe University]

J. Phys. Chem. B., **119**, 263–273, 2015.

Amino acid ionic liquids (AAILs) are gaining attention because of their potential in CO₂ capture technology. Molecular dynamics simulations of AAILs tetramethylammonium glycinate ([N1111][Gly]), tetrabutylammonium glycinate ([N4444][Gly]), and 1,1,1-trimethylhydrazinium glycinate ([A1111][Gly]) and their corresponding mixtures with water were performed to investigate the effect of water concentration on the cation–anion interactions. The water content significantly influenced the free volume (FV) and fractional free volume (FFV) of the AAILs that varied with the hydrophobic and hydrophilic nature of the ion pairs.

Coarse-Grained Model of Glycosaminoglycans

Sergey A. Samsonov, Leon Bichmann, M. Teresa Pisabarro [BIOTEC TU Dresden]

J.Chem. Infor. and Mod. **55**, 114–124, 2015.

Glycosaminoglycans (GAGs) represent a class of anionic periodic linear polysaccharides, which mediate cell communication processes by interactions with their protein targets in the extracellular matrix. Due to their high flexibility, charged nature, periodicity, and polymeric nature, GAGs are challenging systems for computational approaches. To deal with the length challenge, CG modeling could be a promising approach. In this work, we develop AMBER-compatible CG parameters for GAGs using all-atomic (AA) MD simulations in explicit solvent and the Boltzmann conversion approach.

Exploring a Non-ATP Pocket for Potential Allosteric Modulation of PI3K α

Paraskevi Gkeka, Alexandra Papafotika, Savvas Christoforidis, Zoe Cournia [Academy of Athens]

J. Phys. Chem. B., **119**, 1002–1016, 2015.

Allosteric modulators offer a novel approach for kinase inhibition because they target less conserved binding sites compared to the active site; thus, higher selectivity may be obtained. PIK-108, a known pan phosphoinositide 3-kinase (PI3K) inhibitor, was recently detected to occupy a non-ATP binding site in the PI3K α C-lobe. This newly identified pocket is located close to residue 1047, which is frequently mutated in human cancers (H1047R). In order to assess the interactions, stability, and any possible allosteric effects of this inhibitor on PI3K α , extensive MD simulations in aqueous solution were performed for the wild type (WT) human, WT murine, and H1047R human mutant PI3K α proteins.

Molecular Dynamics (Cont'd)

Molecular Mechanism of Myoglobin Autoxidation: Insights from Computer Simulations

J. P. Arcon, P. Rosi, A. A. Petruk, M. A. Marti, D. A. Estrin
[Universidad de Buenos Aires]

J. Phys. Chem. B., **119**, 1802–1813, 2015.

Myoglobin (Mb) and hemoglobin have the biological ability to carry/store oxygen (O₂), a property which requires its heme iron atom to be in the ferrous -Fe(II)-state. However, the thermodynamically stable state in the presence of O₂ is Fe(III) and thus the oxidation rate of a globin is a critical parameter related to its function. Site directed mutants in residues 29 (B10), which shapes the distal cavity, and 64 (E7), the well-known histidine gate, have been shown to display a wide range of autoxidation rate constants. In this work, we have thoroughly studied the mechanism underlying the autoxidation process by means of state-of-the-art computer simulation methodologies, using Mb and site directed mutants as benchmark cases.

Free Energy Perturbation

Rapid Alchemical Free Energy Calculation Employing a Generalized Born Implicit Solvent Model

Katja Ostermeir, Martin Zacharias [Technische Universität München]

J. Phys. Chem. B., **119**, 968–975, 2015.

Generalized Born (GB) implicit solvent models are typically used in postprocessing of molecular dynamics trajectories obtained from explicit solvent simulations to estimate binding free energies or effects of mutations in proteins. The possibility to employ a GB implicit solvent model for the calculation of rigorous free energy changes associated with alchemical transformations has been explored. During free energy perturbation (FEP) simulations, Lennard-Jones, Coulomb, and Born radii parameters are transformed gradually in a single-topology series. The FEP calculations are embedded in a replica exchange scheme allowing rapid convergence.

Distinguishing Binders from False Positives by Free Energy Calculations: Fragment Screening Against the Flap Site of HIV Protease

Nanjie Deng, Stefano Forli, Peng He, Alex Perryman, Lauren Wickstrom, R. S. K. Vijayan, Theresa Tiefenbrunn, David Stout, Emilio Gallicchio, Arthur J. Olson, Ronald M. Levy [Temple University]

J. Phys. Chem. B., **119**, 976–988, 2015.

Molecular docking is a powerful tool used in drug discovery and structural biology for predicting the structures of ligand–receptor complexes. However, the accuracy of docking calculations can be limited by factors such as the neglect of protein reorganization in the scoring function; as a result, ligand screening can produce a high rate of false positive hits. Although absolute binding free energy methods still have difficulty in accurately rank-ordering binders, we believe that they can be fruitfully employed to distinguish binders from nonbinders and reduce the false positive rate. Here we study a set of ligands that dock favorably to a newly discovered, potentially allosteric site on the flap of HIV-1 protease.

QM and QM/MM

Improving the Q2MM method for transition state force field modeling

Elaine Limé , Per-Ola Norrby [University of Gothenburg]

J. Comp. Chem., **36**, 244–250, 2015.

The Quantum-to-molecular mechanics method (Q2MM) for converting quantum mechanical transition states (TSs) to molecular mechanical minima has been modified to allow a fit to the “natural” reaction mode eigenvalue. The resulting force field gives an improved representation of the energy curvature at the TS, but can potentially give false responses to steric interactions. Ways to address this problem while staying close to the “natural” TS force field are discussed.

DFT studies on armchair (5, 5) SWCNT functionalization. Modification of selected structural and spectroscopic parameters upon two-atom molecule attachment

Marzena Jankowska, Teobald Kupka, Leszek Stobiński, Jakub Kaminský [Czech Academy of Sciences]

J. Mol.Graph. and Mod., **55**,105-114,2015.

Density functional theory (DFT) studies on adsorption of several gaseous homo- and hetero-diatom molecules (AB) including H₂, O₂, N₂, NO and CO on external surface of H-capped pristine armchair (5, 5) single-walled carbon nanotube (SWCNT) were conducted. Structures of C₇₀H₁₀ and the corresponding C₇₀H₁₀-AB adducts were fully optimized at the B3LYP/6-311G* level of theory. Calculated HOMO/LUMO energy gaps (E_g), ¹³C NMR chemical shifts and IR/Raman parameters were analyzed and critically compared with available experimental data.

Basis Set Generation for Quantum Dynamics Simulations Using Simple Trajectory-Based Methods

Maximilian A. C. Saller ,Scott Habershon [University of Warwick]

J. Chem. Theor. and Comp, **11**, 8–16, 2015.

Methods for solving the time-dependent Schrödinger equation generally employ either a global static basis set, which is fixed at the outset, or a dynamic basis set, which evolves according to classical-like or variational equations of motion; the former approach results in the well-known exponential scaling with system size, while the latter can suffer from challenging numerical problems, such as singular matrices, as well as violation of energy conservation. Here, we suggest a middle road: building a basis set using trajectories to place time-independent basis functions in the regions of phase space relevant to wave function propagation.

Characterization of the Three-Dimensional Free Energy Manifold for the Uracil Ribonucleoside from Asynchronous Replica Exchange Simulations

Brian K. Radak, Melissa Romanus, Tai-Sung Lee, Haoyuan Chen, Ming Huang, Antons Treikalis, Vivekanandan Balasubramanian, Shantenu Jha, Darrin M. York [Rutgers University]

J. Chem. Theor. and Comp, **11**, 373–377, 2015.

Replica exchange molecular dynamics has emerged as a powerful tool for efficiently sampling free energy landscapes for conformational and chemical transitions. However, daunting challenges remain in efficiently getting such simulations to scale to the very large number of replicas required to address problems in state spaces beyond two dimensions. In the present work, we explore this problem space by applying asynchronous Hamiltonian replica exchange molecular dynamics with a combined quantum mechanical/molecular mechanical potential to explore the conformational space for a simple ribonucleoside.

QM and QM/MM (Cont'd)

QM/MM Simulations of Amyloid- β 42 Degradation by IDE in the Presence and Absence of ATP

Carlos H. B. da Cruz , G. M. Seabra [Cidade Universitária]

J.Chem. Infor. and Mod. **55**, 72–83, 2015.

The ability of the insulin-degrading enzyme (IDE) to degrade amyloid- β 42 (A β 42), a process regulated by ATP, has been studied as an alternative path in the development of drugs against Alzheimer's disease. In this study, we calculated the potential of mean force for the degradation of A β 42 by IDE in the presence and absence of ATP by umbrella sampling with hybrid quantum mechanics and molecular mechanics (QM/MM) calculations, using the SCC-DFTB QM Hamiltonian and Amber ff99SB force field. Results indicate that the reaction occurs in two steps: The first step is characterized by the formation of the intermediate.

Direct Validation of the Single Step Classical to Quantum Free Energy Perturbation

Christopher Cave-Ayland, Chris-Kriton Skylaris, Jonathan W. Essex [University of Southampton]

J. Phys. Chem. B., **119**, 1017–1025, 2015.

The use of the Zwanzig equation in the calculation of single-step perturbations to provide first-principles (ab initio) quantum mechanics (QM) correction terms to molecular mechanics (MM) free energy cycles is well established. A rigorous test of the ability to converge such calculations would be very useful in this context. In this work, we perform a direct assessment of the convergence of the MM to QM perturbation, by attempting the reverse QM to MM perturbation. This required the generation of extensive QM molecular dynamics trajectories, using density functional theory (DFT), within the representative biological system of a DNA adenosine–thymidine dimer.

Projected Hybrid Orbitals: A General QM/MM Method

Yingjie Wang ,Jiali Gao [Jilin University]

J. Phys. Chem. B., **119**, 1213–1224, 2015.

A projected hybrid orbital (PHO) method was described to model the covalent boundary in a hybrid quantum mechanical and molecular mechanical (QM/MM) system. The PHO approach can be used in ab initio wave function theory and in density functional theory with any basis set without introducing system-dependent parameters. In this method, a secondary basis set on the boundary atom is introduced to formulate a set of hybrid atomic orbitals. The primary basis set on the boundary atom used for the QM subsystem is projected onto the secondary basis to yield a representation that provides a good approximation to the electron-withdrawing power of the primary basis set to balance electronic interactions between QM and MM subsystems.

Atomistic Modeling of Two-Dimensional Electronic Spectra and Excited-State Dynamics for a Light Harvesting 2 Complex

C. P. van der Vegte, J. D. Prajapati, U. Kleinekathöfer, J. Knoester, T. L. C. Jansen [University of Groningen]

J. Phys. Chem. B., **119**, 1302–1313, 2015.

The Light Harvesting 2 (LH2) complex is a vital part of the photosystem of purple bacteria. It is responsible for the absorption of light and transport of the resulting excitations to the reaction center in a highly efficient manner. A general description of the chromophores and the interaction with their local environment is crucial to understand this highly efficient energy transport. Here we include this interaction in an atomistic way using mixed quantum-classical (molecular dynamics) simulations of spectra. In particular, we present the first atomistic simulation of nonlinear optical spectra for LH2 and use it to study the energy transport within the complex.

QM and QM/MM (Cont'd)

Two-Dimensional Near Ultraviolet (2DNUV) Spectroscopic Probe of Structural-Dependent Exciton Dynamics in a Protein

Jun Li, Mingsen Deng, Dmitri V. Voronine, Shaul Mukamel, , Jun Jiang [University of Science and Technology of China]

J. Phys. Chem. B., **119**, 1314–1322, 2015.

Understanding the exciton dynamics in biological systems is crucial for the manipulation of their function. We present a combined quantum mechanics (QM) and molecular dynamics (MD) simulation study that demonstrates how coherent two-dimensional near-ultraviolet (2DNUV) spectra can be used to probe the exciton dynamics in a mini-protein, Trp-cage. The 2DNUV signals originate from aromatic transitions that are significantly affected by the couplings between residues, which determine exciton transport and energy relaxation. The temporal evolution of 2DNUV features captures important protein structural information, including geometric details and peptide orientations.

A QM/MM Free Energy Study of the Oxidation Mechanism of Dihydroorotate Dehydrogenase (Class 1A) from *Lactococcus lactis*

José Rogério A. Silva, Adrian E. Roitberg, Cláudio Nahum Alves [Universidade Federal do Pará, Belém]

J. Phys. Chem. B., **119**, 1468–1473, 2015.

The dihydroorotate dehydrogenase (DHOD) class 1A enzyme catalyzes is the only redox enzyme in the biosynthetic pathway (de novo) of pyrimidines where dihydroorotate (DHO) is oxidized to orotate (OA) coupled to reduction of a flavin mononucleotide (FMN) cofactor. The rupture of two DHO C–H bonds can proceed in a concerted or stepwise way. Herein, the catalytic mechanism of DHOD from *Lactococcus lactis* involving DHO oxidation (first half-reaction) was described using a hybrid quantum mechanics/molecular mechanics (QM/MM) approach and molecular dynamics simulations.

Comparative or Homology Modeling

SIRAH: A Structurally Unbiased Coarse-Grained Force Field for Proteins with Aqueous Solvation and Long-Range Electrostatics

Leonardo Darré, Matías Rodrigo Machado, Astrid Febe Brandner, Humberto Carlos González, Sebastián Ferreira, Sergio Pantano [King's College, London]

J. Chem. Theor. and Comp., **11**, 723–739, 2015.

Modeling of macromolecular structures and interactions represents an important challenge for computational biology, involving different time and length scales. However, this task can be facilitated through the use of coarse-grained (CG) models, which reduce the number of degrees of freedom and allow efficient exploration of complex conformational spaces. This article presents a new CG protein model named SIRAH, developed to work with explicit solvent and to capture sequence, temperature, and ionic strength effects in a topologically unbiased manner. SIRAH is implemented in GROMACS, and interactions are calculated using a standard pairwise Hamiltonian for classical molecular dynamics simulations.

Ligand Docking

Structural Basis of Ligand Binding to UDP-Galactopyranose Mutase from *Mycobacterium tuberculosis* Using Substrate and Tetrafluorinated Substrate Analogues

Karin E. van Straaten, Jijin R. A. Kuttivatveetil, Charlotte M. Sevrain, Sydney A. Villaume, Jesús Jiménez-Barbero, Bruno Linclau, Stéphane P. Vincent, David A. R. Sanders [University of Saskatchewan]

J. Am. Chem. Soc., **137**, 1230–1244, 2015.

UDP-Galactopyranose mutase (UGM) is a flavin-containing enzyme that catalyzes the reversible conversion of UDP-galactopyranose (UDP-Galp) to UDP-galactofuranose (UDP-Galf) and plays a key role in the biosynthesis of the mycobacterial cell wall galactofuran. A soluble, active form of UGM from *Mycobacterium tuberculosis* (MtUGM) was obtained from a dual His6-MBP-tagged MtUGM construct. We present the first complex structures of MtUGM with bound substrate UDP-Galp (both oxidized flavin and reduced flavin).

Molecular recognition of CYP26A1 binding pockets and structure–activity relationship studies for design of potent and selective retinoic acid metabolism blocking agents

Bin Sun, Shuai Song, Chen-Zhou Hao, Wan-Xu Huang, Chun-Chi Liu, Hong-Lei Xie, Bin Lin, Mao-Sheng Cheng, Dong-Mei Zhao [Shenyang Pharmaceutical University]

J. Mol. Graph. and Mod., **56**, 10–19, 2015.

All-trans-retinoic acid (ATRA), the biologically most active metabolite of vitamin A, plays a major role in the regulation of cellular differentiation and proliferation, and it is also an important pharmacological agent particularly used in the treatment of cancer, skin, neurodegenerative and autoimmune diseases. In this study, CYP26A1 and its interactions with retinoic acid-competitive metabolism blocking agents were investigated by a combined ligand- and structure-based approach. First, since the crystal structure of CYP26A1 protein has not been determined, we constructed the 3D structure of CYP26A1 using homology modeling.

Ligand Binding and Functional Selectivity of L-Tryptophan Metabolites at the Mouse Aryl Hydrocarbon Receptor (mAHR)

Roberto Nuti, Marco Gargaro, Davide Matino, Daniela Dolciami, Ursula Grohmann, Paolo Puccetti, Francesca Fallarino, Antonio Macchiarulo [Università di Perugia]

J. Chem. Infor. and Mod. **54**, 3373–3383, 2014.

The aryl hydrocarbon receptor (AhR) is a nuclear receptor regulating a wide range of biological and toxicological effects. Metabolites of L-tryptophan are able to bind and activate AhR, providing a link between tryptophan catabolism and a novel mechanism of protective tolerance, referred to as “disease tolerance”. Combining homology modeling, docking studies, and molecular dynamic simulations with mutagenesis experiments and gene profiling, in this work we report that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and two different L-tryptophan metabolites, namely L-Kynurenine and FICZ (6-formylindolo[3,2-b]carbazole), are able to bind to mAHR, exploiting different key interactions with distinct set of fingerprint residues.

Molecular Dynamics Simulations of Heart-type Fatty Acid Binding Protein in Apo and Holo Forms, and Hydration Structure Analyses in the Binding Cavity

Daisuke Matsuoka, Shigeru Sugiyama, Michio Murata, Shigeru Matsuoka [Osaka University]

J. Phys. Chem. B., **119**, 114–127, 2015.

Intracellular lipid binding proteins (iLBPs) share distinctive features: a rigid protein structure composed of a β -barrel and an α -helix cap, and a large internalized water cluster. Although X-ray crystallographic studies have elucidated the three-dimensional structures of iLBPs, the protein dynamics and the role of the large water cluster in protein function remain unknown. In the present study, we performed molecular dynamics (MD) simulations on human heart-type fatty acid binding protein (FABP3), a typical iLBP that is highly expressed in heart and skeletal muscles, and showed that an altered mode of protein dynamics and rearrangement of the internal water cluster are key elements of ligand binding.

Ligand Docking (Cont'd)

Identification of Ubiquinol Binding Motifs at the Qo-Site of the Cytochrome bc₁ Complex

Angela M. Barragan, Antony R. Crofts, Klaus Schulten, Ilia A. Solov'yov [University of Southern Denmark]

J. Phys. Chem. B., **119**, 433–447, 2015.

Enzymes of the bc₁ complex family power the biosphere through their central role in respiration and photosynthesis. These enzymes couple the oxidation of quinol molecules by cytochrome c to the transfer of protons across the membrane, to generate a proton-motive force that drives ATP synthesis. Key for the function of the bc₁ complex is the initial redox process that involves a bifurcated electron transfer in which the two electrons from a quinol substrate are passed to different electron acceptors in the bc₁ complex. The electron transfer is coupled to proton transfer.

Docking and Free Energy Perturbation Studies of Ligand Binding in the Kappa Opioid Receptor

Dahlia A. Goldfeld, Robert Murphy, Byungchan Kim, Lingle Wang, Thijs Beuming, Robert Abel, Richard A. Friesner [Columbia University]

J. Phys. Chem. B., **119**, 824–835, 2015.

The kappa opioid receptor (KOR) is an important target for pain and depression therapeutics that lack harmful and addictive qualities of existing medications. We present a model for the binding of morphinan ligands and JDTic to the JDTic/KOR crystal structure based on an atomic level description of the water structure within its active site. The model contains two key interaction motifs that are supported by experimental evidence. The first is the formation of a salt bridge between the ligand and Asp 1383.32 in transmembrane domain (TM) 3. The second is the stabilization by the ligand of two high energy, isolated, and ice-like waters near TM5 and TM6.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 55, January, 2015.

- 1-12 **Imidacloprid and thiacloprid neonicotinoids bind more favourably to cockroach than to honeybee $\alpha 6$ nicotinic acetylcholine receptor: Insights from computational studies** ,Balaji Selvam [Université de Nantes], Jérôme Graton, Adèle D. Laurent, Zakaria Alamiddine, Monique Mathé-Allainmat, Jacques Lebreton, Olivier Coqueret, Christophe Olivier, Steeve H. Thany, Jean-Yves Le Questel

See Applications / Ligand Binding.

- 13-24 **Principal Component Analysis reveals correlation of cavities evolution and functional motions in proteins** ,Nathan Desdouits [Institut Pasteur, CNRS - UMR3258], Michael Nilges, Arnaud Blondel

See Applications / Protein Conformational Analysis.

- 25-32 **Theoretical study of the mechanism of protein arginine deiminase 4 (PAD4) inhibition by F-amidine** ,Dongmei Li [Nankai University], Cui Liu, Jianping Lin

See Applications / Enzyme Catalysis.

- 33-40 **Interlayer charge-transfer in impacting the second hyperpolarizabilities: Radical and cation species of hexathiophenalenylium and its nitro dimmers** ,Li Wang, Wen-Yong Wang, Na-Na Ma, Dong-Mei Tian, Jiao Wang, Yong-Qing Qiu[Northeast Normal University]

We performed density functional theory to calculate the binding interactions, electronic absorption spectra and the second hyperpolarizabilities of cation and radical dimers of Hexathiophenalenylium and its nitro derivatives.

- 41-47 **Hydrogen generation from methylamine using silicon carbide nanotubes as a dehydrogenation catalyst: A density functional theory study** ,Mehdi D. Esrafil [University of Maragheh] , Roghaye Nurazar

The adsorption and decomposition of methylamine on the surface of a pristine silicon-carbide nanotube (SiCNT) are investigated by density functional theory calculations. The adsorption energies of possible stable configurations and the activation energies for possible elementary reactions involved are obtained in the present study.

- 48-64 **Long-timescale motions in glycerol-monopalmitate lipid bilayers investigated using molecular dynamics simulation** ,Monika Laner [Laboratory of Physical Chemistry, ETH Zürich], Bruno A.C. Horta, Philippe H. Hünenberger

See Applications / Membrane Proteins and Lipid-Peptide Interactions.

- 65-71 **Ab initio modeling approach towards establishing the structure and docking orientation of the Porphyromonas gingivalis FimA** ,Marni E. Cueno [Nihon University], Keiji Nagano, Kenichi Imai, Muneaki Tamura, Fuminobu Yoshimura, Kuniyasu Ochiai

See Applications / Protein Structure Analysis.

- 72-84 **Secondary structure assignment for conformationally irregular peptides: Comparison between DSSP, STRIDE and KAKSI** ,Yuan Zhang, Celeste Sagui[North Carolina State University]

See Applications / Protein Secondary Structure.

- 85-104 **Effect of methanol on the phase-transition properties of glycerol-monopalmitate lipid bilayers investigated using molecular dynamics simulations: In quest of the biphasic effect** ,Monika Laner, Philippe H. Hünenberger [Laboratory of Physical Chemistry, ETH Zürich]

See Applications / Membrane Proteins and Lipid-Peptide Interactions.

- 105-114 **DFT studies on armchair (5, 5) SWCNT functionalization. Modification of selected structural and spectroscopic parameters upon two-atom molecule attachment** ,Marzena Jankowska, Teobald Kupka, Leszek Stobiński, Jakub Kaminský [Czech Academy of Sciences]

See Methodology / QM and QM/MM.

- 115-122 **Conformational diversity of bacterial FabH: Implications for molecular recognition specificity** ,Pages Anuradha Mittal, Michael E. Johnson[University of Illinois at Chicago]

See Applications / Enzyme Catalysis.

- 123-133 **Revealing halogen bonding interactions with anomeric systems: An ab initio quantum chemical studies**, Rabindranath Lo, Bishwajit Ganguly [CSIR-Central Salt & Marine Chemicals Research Institute]

A computational study has been performed using MP2 and CCSD(T) methods on a series of O...X (X = Br, Cl and I) halogen bonds to evaluate the strength and characteristic of such highly directional noncovalent interactions. The study has been carried out on a series of dimeric complexes formed between interhalogen compounds (such as BrF, BrCl and BrI) and oxygen containing electron donor molecule.

- 134-147 **Structural modeling and docking studies of ribose 5-phosphate isomerase from Leishmania major and Homo sapiens: A comparative analysis for Leishmaniasis treatment** ,Priscila V.S.Z. Capriles [Laboratório Nacional de Computação Científica], Luiz Phillippe R. Baptista, Isabella A. Guedes, Ana Carolina R. Guimarães, Fabio L. Custódio, Marcelo Alves-Ferreira, Laurent E. Dardenne

See Applications / Medicinal Chemistry and Drug Design.

Journal of Molecular Graphics and Modelling, 56, January, 2015.

- 1-9 **Cloning and molecular modeling of a thermostable carboxylesterase from the chicken uropygial glands**, Ahmed Fendri[Laboratoire de Biochimie et de Génie Enzymatique des Lipases], Fakher Frikha, Hanen Louati, Madiha Bou Ali, Hela Gargouri, Youssef Gargouri, Nabil Miled

See Applications / Protein Dynamics.

- 10-19 **Molecular recognition of CYP26A1 binding pockets and structure–activity relationship studies for design of potent and selective retinoic acid metabolism blocking agents**, Bin Sun, Shuai Song, Chen-Zhou Hao, Wan-Xu Huang, Chun-Chi Liu, Hong-Lei Xie, Bin Lin, Mao-Sheng Cheng, Dong-Mei Zhao[Shenyang Pharmaceutical University]

See Methodology / Ligand Docking.

- 20-30 **Exploration of the structural requirements of HIV-protease inhibitors using pharmacophore, virtual screening and molecular docking approaches for lead identification**, Md Ataul Islam, Tahir S. Pillay[University of Pretoria and National Health Laboratory Service]

See Applications / Medicinal Chemistry and Drug Design.

- 31-42 **Rational design of hyper-glycosylated interferon beta analogs: A computational strategy for glycoengineering**, Mojtaba Samoudi, Fatemeh Tabandeh, Zarrin Minuchehr, Reza Ahangari Cohan, Davoud Nouri Inanlou, Mahvash Khodabandeh, Mohammad Sabery Anvar[National Institute of Genetic Engineering and Biotechnology (NIGEB)]

Glycoengineering has been successfully used to improve the physicochemical and pharmaceutical properties of therapeutics. A computational strategy was employed to predict the structural distortions and functional alterations that might be caused by the change in amino acid sequence. Accordingly, three-dimensional (3D) structures of the designed huIFN- β analogs were generated by comparative modeling.

- 43-52 **Structural basis for cooperative binding of azoles to CYP2E1 as interpreted through guided molecular dynamics simulations**, Joseph W. Levy, Jessica H. Hartman, Martin D. Perry Jr., Grover P. Miller[University of Arkansas for Medical Sciences]

CYP2E1 metabolizes a wide array of small, hydrophobic molecules, resulting in their detoxification or activation into carcinogens through Michaelis–Menten as well as cooperative mechanisms. Herein, we employed computational docking studies coupled to molecular dynamics simulations to provide a critical perspective for understanding a structural basis for cooperativity observed for an array of azoles from our previous binding and catalytic studies (Hartman et al., 2014).

- 53-59 **A DFT study of the unusual substrate-assisted mechanism of *Serratia marcescens* chitinase B reveals the role of solvent and mutational effect on catalysis**, Jitrayut Jitnonom [University of Phayao], Chanchai Sattayanon, Nawee Kungwan, Supa Hannongbua

See Applications / Enzyme Catalysis.

- 60-73 **Exploring the drug resistance of V32I and M46L mutant HIV-1 protease to inhibitor TMC114: Flap dynamics and binding mechanism** ,Biswa Ranjan Meher, Yixuan Wang[Albany State University]

See Applications / Medicinal Chemistry and Drug Design.

- 74-83 **DFT studies of the formation of furanoid derivatives of ammonium chlorides** ,Justyna Wielińska, Beata Liberek, Andrzej Nowacki[University of Gdańsk]

B3LYP/6-31+G** level computations were performed on the formation of ammonium salts during the reaction of (S)-1,4-anhydro-5-chloro-2,3,5-trideoxypentitol (1) (2S,5S)-2,5-anhydro-6-chloro-1,3,4,6-tetradeoxyhexitol (2) and methyl 5-chloro-2,3,5-trideoxy- β -D-pentofuranoside (3) with ammonia in order to describe the reaction pathway in detail.

- 84-90 **Using support vector machines to identify protein phosphorylation sites in viruses** ,Shu-Yun Huang, Shao-Ping Shi, Jian-Ding Qiu [Nanchang University], Ming-Chu Liu

See Methodology / Potentials and Parameters.

- 91-102 **Ligand-based modeling followed by in vitro bioassay yielded new potent glucokinase activators** ,Mutaseem O. Taha [The University of Jordan], Maha Habash, Ma'mon M. Hatmal, Ahmed H. Abdelazeem, Amjad Qandil

See Applications / Quantitative Structure-Activity Relations.

- 103-112 **Molecular dynamics simulation and free energy calculation studies of kinase inhibitors binding to active and inactive conformations of VEGFR-2** ,XiaoYun Wu, ShanHe Wan, GuangFa Wang, Hong Jin, ZhongHuang Li, YuanXin Tian, ZhengGuang Zhu, JiaJie Zhang[Southern Medical University]

See Applications / Ligand Binding.

- 113-129 **Ligand-based 3D QSAR analysis of reactivation potency of mono- and bis-pyridinium aldoximes toward VX-inhibited rat acetylcholinesterase** ,Rafael Dolezal, Jan Korabecny, David Malinak, Jan Honegr, Kamil Musilek, Kamil Kuca[University Hospital Hradec Kralove]

See Applications / Quantitative Structure-Activity Relations.

Journal of Computational Chemistry, 36 (3), January, 2015.

- 137–145 **Clarifying and illustrating the electronic energy transfer pathways in trimeric and hexameric aggregation state of cyanobacteria allophycocyanin within the framework of Förster theory** ,Yanliang Ren, Osama Melhem, Yongjian Li, Bo Chi, Xinya Han, Hao Zhu, Lingling Feng, Jian Wan [Central China Normal University] , Xin Xu

Within the framework of the Förster theory, the electronic excitation energy transfer pathways in the cyanobacteria allophycocyanin (APC) trimer and hexamer were studied. The associated physical quantities (i.e., excitation energy, oscillator strength, and transition dipole moments) of the phycocyanobilins (PCBs) located in APC were calculated at time-dependent density functional theory (TDDFT) level of theory.

- 146–150 **Isolated pentagon rule violating endohedral metallofullerenes explained using the Hückel rule: A statistical mechanical study of the C₈₄ Isomeric Set** ,Timothy J. Fuhrer [Radford University] , Angel M. Lambert

Fullerenes and their structure and stability have been a major topic of discussion and research since their discovery nearly 30 years ago. This article presents a systematic, temperature dependent, statistical thermodynamic study of the 24 possible IPR isomers of C₈₄ as well as two of the experimentally known non-IPR isomers (51365 and 51383), at several different charges (0, -2, -4, and -6).

- 151–163 **Theoretical analysis of excited states and energy transfer mechanism in conjugated dendrimers** ,Jing Huang, Likai Du, Deping Hu ,Zhenggang Lan [University of Chinese Academy of Sciences]

The excited states of the phenylene ethynylene dendrimer are investigated comprehensively by various electronic-structure methods. Several computational methods, including SCS-ADC(2), TDHF, TDDFT with different functionals (B3LYP, BH&HLYP, CAM-B3LYP), and DFT/MRCI, are applied in systematic calculations.

- 164–170 **Linear-scaling self-consistent field calculations based on divide-and-conquer method using resolution-of-identity approximation on graphical processing units** ,Takeshi Yoshikawa , Hiromi Nakai [Waseda University]

Graphical processing units (GPUs) are emerging in computational chemistry to include Hartree–Fock (HF) methods and electron-correlation theories. However, *ab initio* calculations of large molecules face technical difficulties such as slow memory access between central processing unit and GPU and other shortfalls of GPU memory. The present study implemented the DC-RI-HF code on GPUs using math libraries, which guarantee compatibility with future development of the GPU architecture.

- 171–180 **Nature of the water/aromatic parallel alignment interactions** ,Mariusz P. Mitoraj, Goran V. Janjić, Vesna B. Medaković, Dušan Ž. Veljković, Artur Michalak, Snežana D. Zarić , Miloš K. Milčić [University of Belgrade]

The water/aromatic parallel alignment interactions are interactions where the water molecule or one of its O—H bonds is parallel to the aromatic ring plane. To investigate the nature of water/aromatic parallel alignment interactions, energy decomposition methods, symmetry-adapted perturbation theory, and extended transition state-natural orbitals for chemical valence (NOCV), were used.

- 181–192 **Symmetry calculation for molecules and transition states** ,Nick M. Vandewiele, Ruben Van de Vijver, Kevin M. Van Geem, Marie-Françoise Reyniers [Universiteit Gent], Guy B. Marin

The symmetry of molecules and transition states of elementary reactions is an essential property with important implications for computational chemistry. This article presents a new algorithm that identifies symmetry of molecules and transition states based on an augmented graph representation of the corresponding structures, in which both topology and the presence of stereocenters are accounted for.

- 193–199 **Semiempirical and DFT computations of the influence of Tb(III) dopant on unit cell dimensions of cerium(III) fluoride** ,Andrii Shyichuk, Marcin Runowski, Stefan Lis [Adam Mickiewicz University] , Jakub Kaczkowski , Andrzej Jezierski

Several computational methods, both semiempirical and *ab initio*, were used to study the influence of the amount of dopant on crystal cell dimensions of CeF₃ doped with Tb³⁺ ions (CeF₃:Tb³⁺). AM1, RM1, PM3, PM6, and PM7 semiempirical parameterization models were used, while the Sparkle model was used to represent the lanthanide cations in all cases.

Journal of Computational Chemistry, 36 (4), January, 2015.

- 201–209 **Communication through molecular bridges: Different bridge orbital trends result in common property trends** ,Jonny Proppe , Carmen Herrmann [Laboratorium für Physikalische Chemie]

Common trends in communication through molecular bridges are ubiquitous in chemistry, such as the frequently observed exponential decay of conductance/electron transport and of exchange spin coupling with increasing bridge length, or the increased communication through a bridge upon closing a diarylethene photoswitch. It appears reasonable to expect the observed common property trends to result from common orbital trends. We illustrate based on a set of model compounds that this assumption is not true, and that common property trends result from either different pairs of orbitals being involved, or from orbital energies not being the dominant contribution to property trends.

- 210–221 **Could the “Janus-like” properties of the halobenzene CX bond (X=Cl, Br) be leveraged to enhance molecular recognition?** ,Krystel El Hage, Jean-Philip Piquemal, Zeina Hobaika, Richard G. Maroun , Nohad Gresh[Saint Joseph University of Beirut]

The CX bond in halobenzenes (X=Cl, Br) exhibits a dual character, being electron-deficient along the CX direction, and electron-rich on its flanks. We sought to amplify both features by resorting to electron-withdrawing and electron-donating substituents, respectively. This was done by quantum chemistry (QC) computations in the recognition sites of three protein targets: farnesyl transferase, coagulation factor Xa, and the HIV-1 integrase.

- 222–234 **An automated method to find transition states using chemical dynamics simulations** ,Emilio Martínez-Núñez [Universidade de Santiago de Compostela]

A procedure to automatically find the transition states (TSs) of a molecular system (MS) is proposed. It has two components: high-energy chemical dynamics simulations (CDS), and an algorithm that analyzes the geometries along the trajectories to find reactive pathways.

- 235–243 **Features of CPB: A Poisson–Boltzmann solver that uses an adaptive cartesian grid** ,Marcia O. Fenley [Florida State University], Robert C. Harris, Travis Mackoy , Alexander H. Boschitsch

PB equations with an ACG, built from a hierarchical octree decomposition of the computational domain. This procedure decreases the number of points required, thereby reducing computational demands. Inside the molecule, CPB solves for the reaction-field component (ϕ_{rf}) of the electrostatic potential (ϕ), eliminating the charge-induced singularities in ϕ .

- 244–250 **Improving the Q2MM method for transition state force field modeling** ,Elaine Limé , Per-Ola Norrby [University of Gothenburg]

See Methodology / QM and QM/MM.

- 251–263 **The Iterative Protein Redesign and Optimization (IPRO) suite of programs** ,Robert J. Pantazes, Matthew J. Grisewood, Tong Li, Nathanael P. Gifford and Costas D. Maranas [University of California]

Proteins are an important class of biomolecules with applications spanning across biotechnology and medicine. In many cases, native proteins must be redesigned to improve various performance metrics by changing their amino acid sequences. Algorithms can help sharpen protein library design by focusing the library on sequences that optimize computationally accessible proxies. The Iterative Protein Redesign and Optimization (IPRO) suite of programs offers an integrated environment.

- 264–271 **BROMOC suite: Monte Carlo/Brownian dynamics suite for studies of ion permeation and DNA transport in biological and artificial pores with effective potentials** ,Pablo M. De Biase [University of Calgary], Suren Markosyan ,Sergei Noskov

See Methodology / Molecular Dynamics.

Journal of Computational Chemistry, 36 (5), January, 2015.

- 273–284 **New algorithms for iterative matrix-free eigensolvers in quantum chemistry** ,Dmitry Zuev, Eugene Vecharynski, Chao Yang, Natalie Orms ,Anna I. Krylov

New algorithms for iterative diagonalization procedures that solve for a small set of eigen-states of a large matrix are described. The performance of the algorithms is illustrated by calculations of low and high-lying ionized and electronically excited states using equation-of-motion coupled-cluster methods with single and double substitutions (EOM-IP-CCSD and EOM-EE-CCSD).

- 285–302 **Quantum-chemistry based calibration of the alkali metal cation series ($\text{Li}^+ - \text{Cs}^+$) for large-scale polarizable molecular mechanics/dynamics simulations** ,Todor Dudev, Mike Devereux, Markus Meuwly, Carmay Lim, Jean-Philip Piquemal ,Nohad Gresh [Université Paris Descartes]

See Applications / Medicinal Chemistry and Drug Design.

- 303–311 **Local response dispersion method in periodic systems: Implementation and assessment**
 ,Yasuhiro Ikabata, Yusuke Tsukamoto, Yutaka Imamura , Hiromi Nakai [Kyoto University]

We report the implementation of the local response dispersion (LRD) method in an electronic structure program package aimed at periodic systems and an assessment combined with the Perdew–Burke–Ernzerhof (PBE) functional and its revised version (revPBE).

- 312–320 **A surface hopping algorithm for nonadiabatic minimum energy path calculations** ,Igor Schapiro [Bowling Green State University], Daniel Roca-Sanjuán, Roland Lindh , Massimo Olivucci

The article introduces a robust algorithm for the computation of minimum energy paths transiting along regions of near-to or degeneracy of adiabatic states. The method facilitates studies of excited state reactivity involving weakly avoided crossings and conical intersections.

- 321–334 **Implementation of a graphical user interface for the virtual multifrequency spectrometer: The VMS-Draw tool** ,Daniele Licari, Alberto Baiardi, Malgorzata Biczysko, Franco Egidi, Camille Latouche ,Vincenzo Barone [Istituto di Chimica dei Composti Organometallici (ICCOM-CNR)]

This article presents the setup and implementation of a graphical user interface (VMS-Draw) for a virtual multifrequency spectrometer. Special attention is paid to ease of use, generality and robustness for a panel of spectroscopic techniques and quantum mechanical approaches.

- 335–347 **Automatic algorithms for completeness-optimization of Gaussian basis sets** ,Susi Lehtola [University of Helsinki]

We present the generic, object-oriented C++ implementation of the completeness-optimization approach (Manninen and Vaara, J. Comput. Chem. 2006, 27, 434) in the freely available ERKALE program, and recommend the addition of basis set stability scans to the completeness-optimization procedure.

- 348–354 **pmx: Automated protein structure and topology generation for alchemical perturbations**
 ,Vytautas Gapsys [Max Planck Institute for Biophysical Chemistry, Göttingen], Servaas Michielssens, Daniel Seeliger , Bert L. de Groot

See Applications / Protein Structure Analysis.

Journal of Molecular Modeling, 21 (1), January, 2015.

- 19 **Direct and solvent-assisted keto–enol tautomerism and hydrogen-bonding interactions in 4-(*m*-chlorobenzylamino)-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one: a quantum-chemical study** .N. Burcu Arslan, Namık Özdemir [Ondokuz Mayıs University]

The tautomeric equilibrium of the title triazole compound was computationally analyzed at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) levels of theory. The solvent effect was considered for three solvents (chloroform, methanol, and water).

- 18 **Nitro and dinitroamino N-oxides of octaazaanthracene as high energy materials** ,Manish Kumar Upadhyay, Soumitra Kumar Sengupta, Hari Ji Singh [DDU Gorakhpur University]

The present study undertook the design of nitro and dinitroamino compounds from the skeleton of isomeric N-oxides of octaazanaphthalene, using computational methods to predict their degradation and explosive characteristics.

- 17 **Computer simulation study of the intermolecular structure of phosphoric acid–N,N-dimethylformamide mixtures** ,Irina V. Fedorova [G. A. Krestov Institute of Solution Chemistry of Russian Academy of Sciences], Michael G. Kiselev, Lyubov P. Safonova

The structures and energies of the complexes $(\text{H}_3\text{PO}_4)_2$, $\text{H}_3\text{PO}_4\text{--DMF}$, and $(\text{H}_3\text{PO}_4)_2\text{--DMF}$ were analyzed at the B3LYP level of approximation. It was found that H-bonds form between H_3PO_4 and DMF molecules, but the strength of the H-bond depends strongly on its molecular environment.

- 16 **Computational studies of water and carbon dioxide interactions with cellobiose** ,Faranak Bazooyar [University of Borås], Martin Bohlén, Kim Bolton

B3LYP/6–311++G** with dispersion correction (DFT-D) was used to study local and global minimum energy structures of water (H_2O) or carbon dioxide (CO_2) bonding with a pair of cellobiose molecules. The calculations showed that neither the H_2O nor the CO_2 prefer to be between the cellobiose molecules, and that the minimum energy structures occur when these molecules bond to the outer surface of the cellobiose pair.

- 15 **Hydrogen bridges of polycyclic aromatic systems with O–H···O bonds — a gas-phase vs. solid-state Car-Parrinello study** ,Jarosław J. Panek, Aneta Jezierska [University of Wrocław]

The current study belongs to a series of investigations of polycyclic aromatic compounds containing intramolecular hydrogen bonds. Close proximity of the coupled aromatic system and hydrogen bridges gives rise to resonance-assisted hydrogen bonding phenomena.

- 14 **Modeling the antiferromagnetic $\text{Mn}^{\text{II}}\text{Mn}^{\text{II}}$ system within the protein phosphatase-5 catalytic site** ,E. A. Salter, R. E. Honkanen, A. Wierzbicki [University of South Alabama]

See Applications / Enzyme Catalysis.

- 13 **Theoretical study of the reaction mechanism of CH_3NO_2 with NO_2 , NO and CO : the bimolecular reactions that cannot be ignored** ,Ji-Dong Zhang [Shihezi University], Li-Hua Kang, Xin-Lu Cheng

The intriguing decompositions of nitro-containing explosives have been attracting interest. While theoretical investigations have long been concentrated mainly on unimolecular decompositions, bimolecular reactions have received little theoretical attention. In this paper, we investigate theoretically the bimolecular reactions between nitromethane (CH_3NO_2)—the simplest nitro-containing explosive—and its decomposition products, such as NO_2 , NO and CO , that are abundant during the decomposition process of CH_3NO_2 .

- 12 **A single theoretical descriptor for the bond-dissociation energy of substituted phenols** ,Carolina Aliaga, Iriux Almodovar, Marcos Caroli Rezende [Universidad de Santiago de Chile]

Relative to the corresponding value of phenol, the bond-dissociation energies (BDE) of substituted phenols correlate well with a single descriptor: the Mulliken charge on the oxygen atom of the phenoxyl radical. Internal reaction coordinates (IRC) for the model reaction of hydrogen abstraction by the hydroperoxyl radical from various 2- and 4-substituted phenols were calculated in order to investigate the role of intra-molecular hydrogen bonds and steric effects on the process.

- 11 **A mixed basis with off-center Gaussian functions for the calculation of the potential energy surfaces for π -stacking interactions: dimers of benzene and planar C_6** , Ersin Yurtsever [Koç University]

A practical mixed basis set was developed to facilitate accurate calculations of potential energy surfaces for π -stacking interactions. Correlation consistent basis sets (cc-PVXZ) were augmented by p-type Gaussian functions placed above and below the planes of C_6 moieties.

- 10 **Theoretical studies of the nitrogen containing compounds adsorption behavior on Na(I)Y and rare earth exchanged RE(III)Y zeolites**, Wei Geng, Haitao Zhang, Xuefei Zhao, Wenyan Zan, Xionghou Gao, Xiaojun Yao [Lanzhou University]

In this work, the adsorption behavior of nitrogen containing compounds including NH_3 , pyridine, quinoline, and carbazole on Na(I)Y and rare earth exchanged La(III)Y, Pr(III)Y, Nd(III)Y zeolites was investigated by density functional theory (DFT) calculations.

- 9 **Molecular dynamics simulation of melting and crystallization processes of polyethylene clusters confined in armchair single-walled carbon nanotubes**, Zhou Zhou, Jinjian Wang, Xiaolei Zhu [Nanjing Tech University], Xiaohua Lu, Wenwen Guan, Yuchen Yang

See Applications / Carbon Nanotubes.

- 8 **Targeting a cluster of arginine residues of neuraminidase to avoid oseltamivir resistance in influenza A (H1N1): a theoretical study**, L. Ramírez-Salinas Gema, L. E. Tolentino-Lopez, F. Martínez-Ramos, I. Padilla-Martínez, J. García-Machorro, J. Correa-Basurto [Instituto Politécnico Nacional]

See Applications / Medicinal Chemistry and Drug Design.

- 7 **Binuclear cyclopentadienylrhenium hydride chemistry: terminal versus bridging hydride and cyclopentadienyl ligands**, Xiaozhen Gao, Nan Li [Beijing Institute of Technology], R. Bruce King, Henry F. Schaefer III

Theoretical studies predict the lowest energy structures of the binuclear cyclopentadienylrhenium hydrides $Cp_2Re_2H_n$ ($Cp = \eta^5-C_5H_5$; $n = 4, 6, 8$) to have a central doubly bridged $Re_2(\mu-H)_2$ unit with terminal η^5-Cp rings and the remaining hydrides as terminal ligands.

- 6 **Theoretical study of the dimerization of aqueous beryllium cations**, Xiaoyan Jin [Fuyang Teachers College], Hai Wu, Hong Wang, Zhengjie Huang, Hong Zhang

The dimerization of monomeric beryllium species was studied via density functional theory (DFT) calculations, and the influences of deprotonation and substitution with various halide anions on the polymerization were explored.

- 5 **Molecular dynamics study on the tensile deformation of cross-linking epoxy resin** ,Dong R. Xin, Qiang Han [South China University of Technology]

Various epoxy resins are used in the electronic industry as encapsulants, adhesive, printed wiring boards, electronic packagings, and so on. In this study, molecular dynamics method is employed to simulate the tensile deformation of the typical electronic epoxy resin.

- 4 **Charge transfer complexes of fullerene[60] with porphyrins as molecular rectifiers. A theoretical study**, Filiberto Montiel, Lioudmila Fomina, Serguei Fomine [Universidad Nacional Autónoma de México]

Molecular diodes based on charge transfer complexes of fullerene[60] with different metalloporphyrins have been modeled. Their current–voltage characteristics and the rectification ratios (RR) were calculated using direct ab initio method at PBE/def2-SVP level of theory with D3 dispersion correction, for voltages ranging from -2 to $+2$ V.

- 3 **An approach to creating a more realistic working model from a protein data bank entry** ,Christopher J. Brandon [University of Colorado], Benjamin P. Martin, Kelly J. McGee, James J. P. Stewart, Sonja B. Braun-Sand

See Applications / Protein Structure Analysis.

- 2 **Effect of water in amorphous polyvinyl formal: insights from molecular dynamics simulation** ,Qiang Yin, Lin Zhang, Bo Jiang, Qinjian Yin, Kai Du [China Academy of Engineering Physics]

In this study, molecular dynamics simulations were performed to study the influence of water on polyvinyl formal. The effects of adding different concentrations of water (0, 0.23, 0.47, 0.94, 1.40, 1.86, 2.76, 3.65 and 4.52 wt%) to a copolymer of polyvinyl acetal, polyvinyl alcohol, and polyvinyl acetate were investigated.

- 1 **Quantum chemical studies on nanostructures of the hydrated methylimidazolium–based ionic liquids**, Hossein Roohi [University of Guilan], Shiva Khyrkah

The B3LYP and M06–2X suits of density functional theory in conjunction with the 6-311++G(2d,2p) basis set were employed to investigate the nanostructures formed from the interaction between water molecules and ionic liquids based on methylimidazolium cation (MIM^+) with the anions ($\text{X}_{1-5} = \text{CH}_3\text{COO}^-$, CF_3COO^- , NO_3^- , BF_4^- , and $\text{N}(\text{CN})_2^-$) on a molecular level.

Journal of Molecular Modeling, 21 (2), February, 2015.

- 32 **Anisotropy and roughness of the solid-liquid interface of BCC Fe**, Yongli Sun, Yongquan Wu [Shanghai University], Xiuming Lu, Rong Li, Junjiang Xiao

Melting point T_m and kinetic coefficient μ (a proportional constant between the interfacial velocity and undercooling ΔT), along with the structural roughness of the solid-liquid interface for body centered cubic (BCC) Fe were calculated by molecular dynamics (MD) simulation.

- 31 **Study on wrinkling in graphene under gradient shear by molecular dynamics simulation**, Jianzhang Huang, Qiang Han [South China University of Technology]

The formation and development mechanisms of wrinkles in a rectangular single layer graphene sheet (SLGS) subjected to in-plane gradient shear displacements are investigated through molecular dynamics (MD) simulations.

- 30 **MaxMod: a hidden Markov model based novel interface to MODELLER for improved prediction of protein 3D models**, Bikram K. Parida, Prasanna K. Panda [CSIR-Institute of Minerals & Materials Technology], Namrata Misra, Barada K. Mishra

See Applications / Protein Structure Analysis.

- 29 **Transport engineering design of AND and NOR gates with a 1,4-2-phenyl-dithiolate molecule**, Aliasghar Shokri [Payame Noor University], Sayed Mohammad Mirzarian

We have explored logical AND and NOR gate responses of a 1,4-2-phenyl-dithiolate molecule threaded by a magnetic flux ϕ in two-terminal junctions by using the Green's function method in the framework of a nearest-neighbor tight-binding approximation.

- 28 **s-Block metallabenzene: aromaticity and hydrogen adsorption**, Rafał Roszak, Szczepan Roszak [Wrocław University of Technology]

Second group metal dimers can replace the carbon atom in benzene to form metallabenzene ($C_5H_6M_2$) compounds. These complexes possess some aromatic character and promising hydrogen adsorption properties. In this study, we investigated the aromatic character of these compounds using aromaticity indices and molecular orbital analysis.

- 27 **First principles investigations of vinazene molecule and molecular crystal: a prospective candidate for organic photovoltaic applications**, Mazmira Mohamad, Rashid Ahmed [Universiti Teknologi Malaysia], Amirudin Shaari, Souraya Goumri-Said

In the present study, DFT approaches are employed to provide an exposition of optoelectronic properties of vinazene molecule and molecular crystal. To gain insight into its properties, different forms of exchange correlation energy functional/potential such as LDA, GGA, BLYP, and BL3YP are used.

- 26 **Theoretical study of the stabilities and detonation performance of 5-nitro-3-trinitromethyl-1H-1,2,4-triazole and its derivatives**, Xueli Zhang, Xuedong Gong [Nanjing University of Science and Technology]

5-Nitro-3-trinitromethyl-1H-1,2,4-triazole (NTMT, A) and its substituted derivatives A-CH₃, A-OCH₃, A-NH₂, A-OH, A-NO₂, and A-ONO₂ were studied using density functional theory (DFT). For all of the molecules except for A-ONO₂, the C-NO₂ bond in the trinitromethyl group was found to be the weakest, and no transition state occurred during the scission of this bond.

- 25 **Some molecular/crystalline factors that affect the sensitivities of energetic materials: molecular surface electrostatic potentials, lattice free space and maximum heat of detonation per unit volume**, Peter Politzer [University of New Orleans], Jane S. Murray

We discuss three molecular/crystalline properties that we believe to be among the factors that influence the impact/shock sensitivities of energetic materials (i.e., their vulnerabilities to unintended detonation due to impact or shock).

- 24 **Atomistic insights into the lung cancer-associated L755P mutation in HER2 resistance to lapatinib: a molecular dynamics study**, Bei Yang, Haiping Zhang, Hao Wang [Tongji University]

See Applications / Medicinal Chemistry and Drug Design.

- 23 **One lithium atom binding with *P*-nitroaniline: lithium salts or lithium electrides?**, Ying Gao, Heng-Qing Wu, Shi-Ling Sun, Hong-Liang Xu, Zhong-min Su [Northeast Normal University]

Recently, both lithium (Li) salts and Li electrides formed by one Li atom interacting with ligand complexes, have been widely investigated. An interesting question emerges: is the configuration of one Li atom interacting with ligand complexes a Li salt or electride? In the present work, four configurations *n*-Li-PNA (*n* = 1–4) were obtained by binding one Li atom with the *p*-nitroaniline (PNA) at different positions to explore this question.

- 22 **Computational prediction for emission energy of iridium (III) complexes based on TDDFT calculations using exchange-correlation functionals containing various HF exchange percentages**, Shengxian Xu, Jinglan Wang, Hongying Xia [Jiangxi Science and Technology Normal University], Feng Zhao, Yibo Wang

The accurate prediction for the emission energies of the phosphorescent Ir (III) complexes is very useful for the realizing of full-color displays and large-area solid-state lighting in OLED fields. Quantum chemistry calculations based on TDDFT methods are most widely used to directly compute the triplet vertical excitation energies, yet sometimes the universality of these calculations can be limited because of the lack of experimental data for the relative family of structural analogues.

- 21 **Theoretical predictions of thermodynamic parameters of adsorption of nitrogen containing environmental contaminants on kaolinite**, Andrea Michalkova Scott [U. S. Army Engineer Research and Development Center (ERDC)], Elizabeth A. Burns, Brandon J. Lafferty, Frances C. Hill

In this study thermodynamic parameters of adsorption of nitrogen containing environmental contaminants (NCCs, 2,4,6, trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), 2,4-dinitroanisole (DNAN), and 3-one-1,2,4-triazol-5-one (NTO)) interacting with the tetrahedral and octahedral surfaces of kaolinite were predicted.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

Abir Haloui
abirhaloui83@yahoo.fr
Department of Chemistry,
Faculty of Sciences, Manar 2,
2092, Tunis, Tunisia

Adam Jarmuła
a.jarmula@nencki.gov.pl
Nencki Institute of Experimental
Biology,
Polish Academy of Sciences,
3 Pasteur St., 02-093, Warszawa,
Poland

Alessandro Erba
alessandro.erba@unito.it
Dipartimento di Chimica IFM and
Centre of Excellence NIS
(Nanostructured Interfaces and
Surfaces),
Università di Torino, Via P. Giuria
5,
Torino I-10125, Italy

Alessandro S. Nascimento
alessandro.nascimento@ufabc.edu.
br
Centro de Engenharia,
Modelagem e Ciências Sociais
Aplicadas,
Universidade Federal do ABC, R.
Santa Adélia,
166, Bangu, Santo Andre,
Sao Paulo 09210-170, Brazil

Alex Bunker
alex.bunker@helsinki.fi
Center for Condensed Matter
Theory,
Department of Physics,
Indian Institute of Science,
Bangalore, India

Ali Ahmadi Peyghan
ahmadi.iau@gmail.com
Young Researchers Club,
Islamic Azad University,
Islamshahr Branch, Tehran, Iran

Amadeu K. Sum
asum@mines.edu
Chemical and Biological
Engineering Department,
Colorado School of Mines, 1600
Illinois Street,
Golden, Colorado, United States

Anastassia N. Alexandrova
ana@chem.ucla.edu
Department of Chemistry and
Biochemistry,
University of California, Los
Angeles,
Los Angeles, California 90095-
1569, United States

Anders Poulsen
anders@colours.dk
S*BIO Pte Ltd, 1 Science Park
Road,
#05-09 The Capricorn,
Singapore Science Park II,
Singapore, 117 528, Singapore

Andreas Bürger
andreas.buerger@rub.de
Institut für Geologie,
Mineralogie und Geophysik,
Ruhr-Universität Bochum,
Universitätsstraße 150,
44801, Bochum, Germany

André H. Juffer
andre.juffer@oulu.fi
Biocenter Oulu and Department of
Biochemistry,
University of Oulu, P.O. Box 3000,
Oulu FI-90014, Finland

Angel E. Garcia
angel@rpi.edu
Department of Physics,
Applied Physics, and Astronomy,
Rensselaer Polytechnic Institute,
110 8th Street, Troy,
New York 12180, United States

Angeles Peña-Gallego
angeles.pena@usc.es
Centro Singular de Investigación
en Química
Biológica e Materiais Moleculares
(CIQUS),
Universidade de Santiago de
Compostela,
Rúa Jenaro de la Fuente, s/n,
Santiago de Compostela, 15782,
Spain

Angelika Baranowska-Lączkowska
angelika.baranowska@ukw.edu.pl
Institute of Physics, Kazimierz
Wielki University,
Plac Weyssenhoffa 11,
PL-85072 Bydgoszcz, Poland

Anil K. Saxena
anilsak@gmail.com
Medicinal and Process Chemistry
Division,

CSIR-Central Drug Research
Institute,
Lucknow, 226001, India

Anna Vulpetti
anna.vulpetti@novartis.com
Novartis Institutes for Biomedical
Research,
Postfach, CH-4002 Basel,
Switzerland

Arumugam Nagarajan
aru.nagarajan@sastra.edu
PSG College of Pharmacy,
Peelamedu,
Coimbatore-641 004, Tamil Nadu,
India

Arun Venkatnathan
arun@iiserpune.ac.in
Department of Chemistry,
Indian Institute of Science
Education and Research,
Dr. Homi Bhabha Road, Pune,
411021, India

Baiqing Li
baiqingli@sdu.edu.cn
Institute of Theoretical Chemistry,
School of Chemistry and Chemical
Engineering,
Key Laboratory of Colloid and
Interface Chemistry (Ministry of
Education),
Shandong University, Jinan,
Shandong,
250100, People's Republic of
China

Banchob Wanno
banchobw@gmail.com
Center of Excellence for
Innovation in
Chemistry and Department of
Chemistry,
Faculty of Science, Mahasarakham
University,
Maha Sarakham, 44150, Thailand

Barada Kanta Mishra
Bioresources Engineering
Department,
CSIR-Institute of Minerals and
Materials Technology,
Bhubaneswar, 751 013, Odisha,
India

Benoit Minisini
bminisini@ismans.fr
ISMANS, 44 Avenue F A
Bartholdi,
72000, Le Mans, France

Benoît Roux,
roux@uchicago.edu

Biosciences Division,
Argonne National Laboratory,
Argonne, Illinois 60439, United
States

Bu-Tong Li, Hai-Shun Wu
butong.lee@gmail.com
School of Chemistry and Material
Science,
Shanxi Normal University,
041004, Linfen, China

C. David Sherrill
sherrill@gatech.edu
Center for Computational
Molecular Science and
Technology,
School of Chemistry and
Biochemistry, and
School of Computational Science
and Engineering,
Georgia Institute of Technology,
Atlanta,
Georgia 30332-0400, United States

C. H. Mak
cmak@usc.edu
Department of Chemistry,
University of Southern California,
Los Angeles, California 90089-
0482,
United States

C. Robert Matthews
C.Robert.Matthews@umassmed.ed
u
Department of Biochemistry &
Molecular Pharmacology,
University of Massachusetts
Medical School,
Worcester, Massachusetts 01605,
United States

Carolina H. Andrade
carolina@farmacia.ufg.br
Laboratório de Planejamento de
Fármacos e Estudos de
Metabolismo
por Modelagem Molecular
(LabMol),
Faculdade de Farmácia,
Universidade Federal de Goiás,
74605-220, Goiania, GO, Brazil

Chandralata Bal
cbal@bitmesra.ac.in
Department of Applied Chemistry,
Birla Institute of Technology,
Mesra,
Ranchi, Jharkhand, 835215, India

Chaoyang Zhang
zcy19710915@yahoo.com.cn
Institute of Chemical Materials,

- China Academy of Engineering Physics (CAEP),
P.O. Box 919-327, Mianyang, Sichuan, China, 621900
- Chen Wang
wangch@nanocr.cn
National Center for Nanoscience and Technology,
11 Beiyitiao Zhongguancun, Beijing 100190, China
- Christopher J. Roberts
cjr@udel.edu
Department of Chemical and Biomolecular Engineering,
University of Delaware, Newark, Delaware 19716, United States
- Claudia Sissi
claudia.sissi@unipd.it
Department of Pharmaceutical and Pharmacological Sciences,
University of Padova, Via Marzolo 5, 3
5131, Padova, Italy
- Cun Xin Wang
College of Life Science and Bioengineering,
Beijing University of Technology, Pingleyuan 100,
Chaoyang District, Beijing, 100124, China
- Daniel P. Aalberts
aalberts@williams.edu
Physics Department, Williams College,
Williamstown, Massachusetts
- Danilo Roccatano
d.roccatano@jacobs-university.de
School of Engineering and Science, Jacobs University Bremen,
Campus Ring 1, 28759 Bremen, Germany
- Danny E. P. Vanpoucke
danny.vanpoucke@ugent.be
SCRiPTS Group,
Department of Inorganic and Physical Chemistry,
Ghent University,
Krijgslaan 281-S3, Gent 9000, Belgium
- Darrin M. York
york@biomaps.rutgers.edu
BioMaPS Institute for Quantitative Biology and
Department of Chemistry and Chemical Biology,
Rutgers University, Piscataway, New Jersey 08854, United States
- David Zanuy
david.zanuy@upc.edu
- Department of Chemical Engineering,
ETSEIB, Universitat Politècnica de Catalunya,
Diagonal 647, 08028, Barcelona, Spain
- Diego Cortés Arriagada
diego.cortesa@usach.cl
Facultad de Química y Biología,
Universidad de Santiago de Chile, Avenida Libertador Bernardo O'Higgins 3363.
Estación Central, Santiago, Chile
- Dieter Langosch
langosch@lrz.tum.de
Lehrstuhl Chemie der Biopolymere,
Technische Universität München, Weihenstephaner Berg 3, and
Munich Center For Integrated Protein Science (CIPSM), 85354 Freising, Germany
- Dmitri K. Klimov
dklimov@gmu.edu
School of Systems Biology, George Mason University,
Manassas, VA, 20110, USA
- Domenico Bordo
domenico.bordo@istge.it
IRCCS Azienda Ospedaliera Universitaria San Martino—IST—Istituto Nazionale Ricerca sul Cancro,
16132 Genova, Italy
- Dong-Qing Wei
dqwei@sjtu.edu.cn
State Key Laboratory of Microbial Metabolism and
College of Life Science and Biotechnology,
Shanghai Jiao Tong University, Shanghai 200240, Minhang District, China
- Dragos Horvath
dhorvath@unistra.fr
Université de Strasbourg,
1 rue B. Pascal,
Strasbourg 67000, France
- Edward L. Loechler
loechler@bu.edu
Biology Department,
Boston University, Boston, MA 02215, United States
- Emili Besalú
emili.besalu@udg.edu
Institute of Computational Chemistry,
University of Girona,
Girona 17071 (Catalonia), Spain
- Ernesto Chigo Anota
echigoa@yahoo.es
Facultad de Ingeniería Química, Benemérita Universidad Autónoma de Puebla,
Av. San Claudio y 18 Sur, 72570, Puebla, Mexico
- Ernesto Chigo Anota
echigoa@yahoo.es
Facultad de Ingeniería Química, Benemérita Universidad Autónoma de Puebla,
C.U. San Manuel., C. P. 72570, Puebla, Mexico
- Farhan Ahmad Pasha
fpasha@rediffmail.com
Applied Chemistry and Physical Chemistry Division,
Institut Français du Pétrole (IFP), 1 et 4 rue Bois Préau, 92582, Rueil Malmaison, France
- Feng-Yin Li
feng64@nchu.edu.tw
Department of Chemistry,
National Chung Hsing University, Taichung, Taiwan 402, Republic of China
- Fernanda Borges
fborges@fc.up.pt
CIQ, Departamento de Química e Bioquímica,
Faculdade de Ciências, Universidade do Porto,
Porto 4169-007, Portugal
- Frank M. Raushel
raushel@tamu.edu
Department of Biochemistry & Biophysics,
Texas A&M University,
College Station, Texas 77843, United States
- Fredrik Pettersson
fredrik_pettersson@mail.se
NeuroSearch Sweden AB,
Arvid Wallgrens Backe 20, S-413 46 Göteborg, Sweden
- George Harauz
gharauz@uoguelph.ca
Department of Molecular and Cellular Biology,
University of Guelph, 50 Stone Road East,
Guelph, Ontario N1G 2W1, Canada
- Gilles Ohanessian
gilles.ohanessian@polytechnique.fr
Laboratoire des Mécanismes Réactionnels,
Department of Chemistry,
Ecole Polytechnique, CNRS, 91128 Palaiseau Cedex, France
- Gleb V. Baryshnikov
glebchem@rambler.ru
Bohdan Khmelnytsky National University,
18031, Cherkasy, Ukraine
- Gloria I. Cárdenas-Jirón
gloria.cardenas@usach.cl
Theoretical Chemistry Laboratory, Faculty of Chemistry and Biology, University of Santiago de Chile (USACH),
Casilla 40, Correo 33, Santiago, Chile
- Glória Regina Franco
gfrancofmg@gmail.com
Laboratório de Genética Bioquímica,
Departamento de Bioquímica e Imunologia,
Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais,
Belo Horizonte, Minas Gerais, Brazil
- Grażyna Nowicka
gwnow@amu.edu.pl
Faculty of Chemistry,
Adam Mickiewicz University, Grunwaldzka 6, 60-780, Poznań, Poland
- Gregory A. Voth
gavoth@uchicago.edu
Department of Chemistry, James Franck Institute, Institute for Biophysical Dynamics and Computation Institute, University of Chicago, 5735 S. Ellis Ave.,
Chicago, Illinois 60637, United States
- Gregory A. Voth
gavoth@uchicago.edu
Department of Chemistry, James Franck Institute, Institute for Biophysical Dynamics and Computation Institute, University of Chicago, Chicago Illinois 60637, United States
- Gundampati Ravi Kumar
ravi_33102000@yahoo.com
School of Biochemical Engineering,
Institute of Technology, Banaras Hindu University,
Varanasi, 221005, India
- Gunturu Krishna Chaitanya
krishnachaitanya.gunturu@gmail.com
School of Chemical Sciences, SRTM University,

Nanded, 431 606, India

Guohui Li
ghli@dicp.ac.cn
Laboratory of Molecular Modeling
and Design,
State Key Laboratory of Molecular
Reaction Dynamics,
Dalian Institute of Chemical
Physics,
Chinese Academy of Sciences,
Dalian,
116023, Liaoning Province,
People's Republic of China

Günther H. Peters
ghp@kemi.dtu.dk
Department of Chemistry,
Technical University of Denmark,
2800 Kgs. Lyngby, Denmark

Hai-Liang Zhu
zhuhl@nju.edu.cn
State Key Laboratory of
Pharmaceutical Biotechnology,
Nanjing University, Nanjing
210093, PR China

Hajime Hirao
hirao@ntu.edu.sg
Division of Chemistry and
Biological Chemistry,
School of Physical and
Mathematical Sciences,
Nanyang Technological University,
21 Nanyang Link, Singapore
637371

He Ming Xiao
xiao@mail.njust.edu.cn
Molecule and Material
Computation Institution,
Nanjing University of Science and
Technology,
Nanjing, 210094, People's
Republic of China

Holger Gohlke
gohlke@uni-duesseldorf.de
Department of Mathematics and
Natural Sciences,
Institute for Pharmaceutical and
Medicinal Chemistry,
Heinrich-Heine-University,
Düsseldorf, Germany

Hossein Shahbani Zahiri
shahbani@nigeb.ac.ir
Department of Molecular Genetics,
National Institute of Genetic
Engineering and Biotechnology
(NIGEB),
Tehran 14155-6343, Iran

Hualiang Jiang
hljiang@mail.shcnc.ac.cn
Drug Discovery and Design
Center,

State Key Laboratory of Drug
Research,
Shanghai Institute of Materia
Medica,
Chinese Academy of Sciences,
555 Zuchongzhi Road, Shanghai
201203, China

Huayong Chen
hychscut@gmail.com
School of Bioscience &
Bioengineering,
South China University of
Technology,
Guangzhou, 510006,
Guangdong, People's Republic of
China

Hwangseo Park
hspark@sejong.ac.kr
Department of Bioscience and
Biotechnology,
Sejong University, 98 Kunja-Dong,
Kwangjin-Ku, Seoul 143-747,
South Korea

Hwanky Lee
leeh@dankook.ac.kr
Department of Chemical
Engineering,
Dankook University, Yongin,
448-701, South Korea

Hyungdon Yun
hyungdon@ynu.ac.kr
School of Biotechnology,
Yeungnam University,
Gyeongsan, South Korea

Jacek Koput
koput@amu.edu.pl
Department of Chemistry,
Adam Mickiewicz University,
60-780 Poznań, Poland

Jaime Rubio-Martinez
jaime.rubio@ub.edu
Department of Physical Chemistry,
University of Barcelona and the
Institut de
Recerca en Química Teòrica i
Computacional (IQTCUB),
Barcelona, Spain

James J. P. Stewart
MrMopac@openmopac.net
Stewart Computational Chemistry,
15210 Paddington Circle,
Colorado Springs, CO, 80921,
USA

Jeffrey Skolnick
skolnick@gatech.edu
Center for the Study of Systems
Biology,
School of Biology,
Georgia Institute of Technology,
250 14th Street, N.W., Atlanta,
Georgia 30318, United States

Jian Fen Fan
jffan@suda.edu.cn
College of Chemistry,
Chemical Engineering and
Materials Science,
Soochow University, Suzhou,
215123, People's Republic of
China

Jianwei Zhao
zhaojw@nju.edu.cn
Key Laboratory of Analytical
Chemistry for Life Science,
School of Chemistry and Chemical
Engineering,
Nanjing University, Nanjing
210008,
People's Republic of China

Jin Yong Lee
jinylee@skku.edu
Department of Chemistry,
Sungkyunkwan University,
Suwon 440-746, Korea

Jing-xiang Zhao
xjz_hmily@yahoo.com.cn
Key Laboratory for Photonic and
Electronic Bandgap Materials,
Ministry of Education,
Harbin Normal University,
Harbin 150025, China

Jiří Kessler, Martin Dračinský and
Petr Bouř
kessler@uochb.cas.cz
Institute of Organic Chemistry and
Biochemistry,
Academy of Sciences,
Flemingovo Náměstí 2,
Prague 166 10, Czech Republic

Joakim P. M. Jämbek
jambeck@me.com
Division of Physical Chemistry,
Arrhenius Laboratory, Stockholm
University,
Stockholm, SE-10691, Sweden

Johannes Kästner
kaestner@theochem.uni-
stuttgart.de
Computational Biochemistry
Group,
Institute of Theoretical Chemistry,
University of Stuttgart,
Pfaffenwaldring 55,
D-70569 Stuttgart, Germany

Josep M. Porta
porta@iri.upc.edu
Institut de Robòtica i Informàtica
Industrial,
UPC-CSIC, Llorens Artigas 4-6,
08028 Barcelona, Spain

Ju-Guang Han

National Synchrotron Radiation
Laboratory,
University of Science and
Technology of China,
230029, Hefei, People's Republic
of China

Ju-Guang Han
jghan@ustc.edu.cn
National Synchrotron Radiation
Laboratory,
University of Science and
Technology of China,
Hefei, 230029, People's Republic
of China

Juan C. Mejuto
xmejuto@uvigo.es
Department of Physical Chemistry,
Faculty of Sciences,
University of Vigo,
32004 Ourense, Spain

Julie D. Forman-Kay
forman@sickkids.ca
Molecular Structure & Function
Program,
Hospital for Sick Children,
Toronto,
ON M5G 1X8, Canada

Julio Caballero
jmcr77@yahoo.com
Centro de Bioinformática y
Simulación Molecular,
Universidad de Talca, 2 Norte 685,
Casilla 721, Talca, Chile

Karel Palát
palat@faf.cuni.cz
Department of Inorganic and
Organic Chemistry,
Charles University in Prague,
Faculty of Pharmacy in Hradec
Kralove,
500 05 Hradec Kralove, Czech
Republic

Karl N. Kirschner
karl.kirschner@scai.fraunhofer.de
Department of Simulation
Engineering,
Fraunhofer-Institute for Algorithms
and
Scientific Computing (SCAI),
Schloss Birlinghoven, 53754,
Sankt Augustin, Germany

Kathleen E. Rogers
krogers@ucsd.edu
Center for Theoretical Biological
Physics,
University of California San Diego,
La Jolla,
California 92093-0365, United
States

Kenneth A. Marx
Department of Chemistry,

University of Massachusetts Lowell, Lowell, MA, 01854, USA	Lijiao Zhao zhaolijiao@bjut.edu.cn College of Life Science and Bioengineering, Beijing University of Technology, Beijing, 100124, China	Matteo Dal Peraro matteo.dalperaro@epfl.ch Laboratory for Biomolecular Modeling, Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Switzerland	Ming Lu lumingchem@163.com School of Chemical Engineering, Nanjing University of Science & Technology, Nanjing, 210094, People's Republic of China
Keun Woo Lee kwlee@gnu.ac.kr Division of Applied Life Science (BK21 Program), Systems and Synthetic Agrobiotech Center (SSAC), Plant Molecular Biology and Biotechnology Research Center (PMBBRC), Research Institute of Natural Science (RINS), Gyeongsang National University (GNU), 501 Jinju-daero, Gazha-dong, Jinju, 660-701, Republic of Korea	Liuping Chen cesclp@mail.sysu.edu.cn KLGHEI of Environment and Energy Chemistry, School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou, 510275, People's Republic of China	Matteo Masetti matteo.masetti4@unibo.it Department of Pharmacy and Biotechnology, Alma Mater Studiorum, Università di Bologna, Via Belmeloro 6, 40126 Bologna, Italy	Ming Wah Wong chmwmw@nus.edu.sg Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore, 117543, Singapore
Kiatatwee Choowongkamon fsciktc@ku.ac.th Department of Biochemistry, Faculty of Science, Kasetsart University, 50 Phaholyothin Rd, Chatuchak, Bangkok, 10900, Thailand	Majda Sekkal-Rahal majsekkal@msn.com L2MSM, Faculté des Sciences, Université Djillali Liabes de Sidi Bel Abbes, B.P. 89, 22000, Sidi Bel Abbes, Algeria	Matthias Rarey rarey@zbh.uni-hamburg.de Center for Bioinformatics, University of Hamburg, Bundesstr. 43, 20146, Hamburg, Germany	Mingsheng Tang mstang@zsu.edu.cn The College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province 450001, PR China
Klaus Schulten kschulte@ks.uiuc.edu Beckman Institute and Department of Physics, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States	Manfred T. Reetz reetz@mpi-muelheim.mpg.de Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany	Mehrnoosh Arrar marrar@ucsd.edu Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California 92093-0365, United States	Minyong Li mli@sdu.edu.cn Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (MOE), School of Pharmacy, Shandong University, Jinan, Shandong 250012, China
Krishna Misra krishnamisra@hotmail.com Center of Biomedical Magnetic Resonance, Lucknow, 226016, India	Marcus C. Durrant marcus.durrant@northumbria.ac.uk Faculty of Health and Life Sciences, Northumbria University, Ellison Building, Newcastle-upon-Tyne NE1 8ST, United Kingdom	Michael I. Sadowski msadows@nimr.mrc.ac.uk MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London NW71AA, United Kingdom	Mohammad Hossein Karimi-Jafari mhkarimijafari@ut.ac.ir Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, Tehran, Iran
Kumar Vanka k.vanka@ncl.res.in Physical Chemistry Division, National Chemical Laboratory, Dr. Homi Bhabha Road, Pashan, Pune, Maharashtra, 411 008, India	Maria J. Ramos mjramos@fc.up.pt REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007, Porto, Portugal	Michael T. Henzl henzlm@missouri.edu Department of Biochemistry, 117 Schweitzer Hall, University of Missouri, Columbia, MO 65211, USA	Mohammad K. Mohammadi mohammadi@iauhavaz.ac.ir Faculty of Sciences, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran
Lennart Nilsson Lennart.Nilsson@ki.se Department of Biosciences and Nutrition, Center of Biosciences, Karolinska Institutet, SE-141 83 Huddinge, Sweden	Mariusz Paweł Mitoraj mitoraj@chemia.uj.edu.pl Department of Theoretical Chemistry, Faculty of Chemistry, Jagiellonian University, R. Ingardena 3, 30-060 Cracow, Poland	Michele Vendruscolo Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom	Mohammad T. Baei baei52@yahoo.com Department of Chemistry, Azadshahr Branch, Islamic Azad University, Azadshahr, Golestan, Iran
Liang Bian bianliang55551@126.com Xinjiang Key Laboratory of Electronic Information Materials and Devices, Xinjiang Technical Institute of Physics & Chemistry, Chinese Academy of Sciences, Urumqi, 830011, China	Matheus P. Freitas matheus@dqf.ufba.br Department of Food Science, Federal University of Lavras, P.O. Box 3037, 37200-000 Lavras, MG, Brazil	Mine Yurtsever mine@itu.edu.tr Department of Chemistry, Istanbul Technical University, Maslak, 34469, Istanbul, Turkey	Mohammad T. Baei baei52@yahoo.com Department of Chemistry, Azadshahr Branch, Islamic Azad University, Azadshahr, Golestan, Iran
		Ming Li liming@swu.edu.cn School of Chemistry and Chemical Engineering, Southwest University, Chongqing, 400715, China	Moisés Elías Domínguez moises@zedat.fu-berlin.de Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195, Berlin, Germany

- Muthusamy Karthikeyan
mkbioinformatics@gmail.com
Department of Bioinformatics,
Science Block, Alagappa
University,
Karaikudi, 630 004, Tamil Nadu,
India
- N. Latha
lata@bic-svc.ac.in
Bioinformatics Infrastructure
Facility,
Sri Venkateswara College
(University of Delhi),
Benito Juarez Road,
Dhaura Kuan, New Delhi 110 021,
India
- Namik Özdemir
namiko@omu.edu.tr
Department of Physics,
Faculty of Arts and Sciences,
Ondokuz Mayıs University,
55139, Kurupelit, Samsun, Turkey
- Nathalie Basdevant
nbasdeva@univ-evry.fr
Laboratoire Analyse et
Modélisation pour la Biologie et
l'Environnement,
UMR8587 CNRS-UEVE-CEA,
Université d'Evry-Val-d'Essonne,
Bd François Mitterrand,
91025 Evry Cedex, France
- Om Silakari
omsilakari@rediffmail.com
Molecular Modeling Lab (MML),
Department of Pharmaceutical
Sciences and Drug Research,
Punjab University, Patiala,
Punjab 147002, India
- Orlando Acevedo
orlando.acevedo@auburn.edu
Department of Chemistry and
Biochemistry,
Auburn University, Auburn,
Alabama 36849, United States
- P. Ravi
rpiitb@hotmail.com
Advanced Centre of Research in
High Energy Materials,
University of Hyderabad,
Hyderabad, 500 046, India
- Patrick R. Onck
P.R.Onck@rug.nl
Micromechanics of Materials,
Zernike Institute for Advanced
Materials,
University of Groningen,
9747 AG Groningen, The
Netherlands
- Pavel M. Polestshuk
polestshuk@bk.ru
Department of Chemistry,
- Moscow State University,
Russian Federation, Moscow,
Russia
- Pei Tang
TangP@anes.upmc.edu
Pittsburgh Supercomputing Center,
Pittsburgh, Pennsylvania 15213,
United States
- Peng Zho
p_zhou@uestc.edu.cn
Center of Bioinformatics (COBI),
School of Life Science and
Technology,
University of Electronic Science
and
Technology of China (UESTC),
Chengdu, 610054, China
- Peter Eastman
peastman@stanford.edu
Department of Bioengineering,
Stanford University, Stanford,
California 94035, United States
- Phool C. Mishra
pcmishra_in@yahoo.com
Department of Physics,
Banaras Hindu University,
Varanasi, 221 005, India
- Ponmalai Kolandaiyel
Department of Physics,
Bharathiar University,
Coimbatore, 641046, India
- Ponnambalam Venuvanalingam
venuvanalingam@yahoo.com
School of Chemistry,
Bharathidasan University,
Tiruchirappalli, 620024, India
- Qiang Cui
cui@chem.wisc.edu
Graduate Program in Biophysics,
University of Wisconsin,
Madison, Wisconsin
- Qiang Zhang
zhangqiang@bhu.edu.cn
Institute of Chemistry,
Chemical engineering and food
safety,
Bohai University, Jinzhou, 121000,
China
- Qingzhong Li
liqingzhong1990@sina.com
The Laboratory of Theoretical and
Computational Chemistry,
Chemistry and Chemical
Engineering College,
Yantai University, Yantai, 264005,
People's Republic of China
- Que-Tien Tran
que-tien.tran@novartis.com
- Novartis Institutes for BioMedical
Research, Inc.,
250 Massachusetts Avenue,
Cambridge, MA 02139
- Radu Silaghi-Dumitrescu
rsilaghi@chem.ubbcluj.ro
Department of Chemistry and
Chemical Engineering,
Babes-Bolyai University,
11 Arany Janos str, Cluj-Napoca,
400028, Romania
- Rafik Karaman
dr_karaman@yahoo.com
Department of Bioorganic
Chemistry,
Faculty of Pharmacy,
Al-Quds University,
PO Box 20002, Jerusalem, Israel
- Ramesh C. Deka
ramesh@tezu.ernet.in
Department of Chemical Sciences,
Tezpur University, Napaam,
Tezpur, 784028, Assam, India
- Ravi Radhakrishnan
rradhak@seas.upenn.edu
Department of Bioengineering,
University of Pennsylvania,
Philadelphia, USA
- Richard Lavery
richard.lavery@ibcp.fr
Bases Moléculaires et Structurales
des Systèmes Infectieux,
Univ. Lyon I/CNRS UMR 5086,
IBCP,
7 Passage du Vercors, 69367 Lyon,
France
- Rifaat Hilal
rhilal@kau.edu.sa
Chemistry Department,
Faculty of Science, KAU,
Jeddah, Saudi Arabia
- Robert A. Evarestov
re1973@re1973.spb.edu
Department of Chemistry,
Quantum Chemistry Division,
St. Petersburg State University,
Universitetsky Prospekt 26,
St. Petersburg 198504, Petergof,
Russia
- Saied M. Soliman
Saied1soliman@yahoo.com
Department of Chemistry,
Faculty of Science, Alexandria
University,
PO Box 426, Ibrahimia, 21525,
Alexandria, Egypt
- Sandeep Patel
sapatel@udel.edu
Department of Chemistry and
Biochemistry,
- University of Delaware,
Newark, Delaware 19716
- Sarel J. Fleishman and Amir
Aharoni
Sarel@weizmann.ac.il
Department of Biological
Chemistry,
Weizmann Institute of Science,
Rehovot 76100, Israel
- Sebahaddin Alptekin
salptekin@karatekin.edu.tr
Department of Physics,
Çankırı Karatekin University,
Cankiri, 18100, Turkey
- Sebastian Kmiecik
sekmi@chem.uw.edu.pl
Laboratory of Theory of
Biopolymers,
Faculty of Chemistry,
University of Warsaw,
Pasteura 1, 02-093 Warsaw, Poland
- Serguei Fomine
fomine@servidor.unam.mx
Instituto de Investigaciones en
Materiales,
Universidad Nacional Autónoma
de México,
Apartado Postal 70-360, CU,
Coyoacán, Mexico DF, 04510,
Mexico
- Serguei Fomine
fomine@servidor.unam.mx
Instituto de Investigaciones en
Materiales Universidad Nacional
Autonoma de Mexico,
Apartado Postal 70-360, CU,
Coyoacan, Mexico DF, 04510,
Mexico
- Sharon Hammes-Schiffer
shs3@illinois.edu
Department of Chemistry,
University of Illinois at Urbana-
Champaign,
600 South Mathews Avenue,
Urbana,
Illinois 61801, United States
- Shyi-Long Lee
chesll@ccu.edu.tw
Department of Chemistry and
Biochemistry,
National Chung Cheng University,
ChiaYi, 621, Taiwan
- Siewert J. Marrink
s.j.marrink@rug.nl
Groningen Biomolecular Sciences
and Biotechnology Institute and
Zernike Institute for Advanced
Materials,
University of Groningen,
Nijenborgh 7,

- 9747 AG Groningen, The Netherlands
Sissades Tongshima
sissades@biotec.or.th
National Center for Genetic Engineering and Biotechnology, 113 Thailand Science Park, Phahonyothin Road, Khlong Nueng, Khlong Luang, Pathum Thani, 12120, Thailand
- Srabani Taraphder
srabani@chem.iitkgp.ernet.in
Department of Chemistry, Indian Institute of Technology, Kharagpur, 721302, India
- Stanley I. Sandler
sandler@udel.edu
Department of Chemical and Biomolecular Engineering, Center for Molecular and Engineering Thermodynamics, University of Delaware, Newark, Delaware 19716
- Suk Bong Hong
sbhong@postech.ac.kr
Department of Chemical Engineering and School of Environmental Science and Engineering, POSTECH, Pohang 790-784, Korea
- Supot Hannongbua
supot.h@chula.ac.th
Research Center for Computational Science, Institute for Molecular Science, Okazaki, Aichi 444-8585, Japan
- Takao Tsuneda
ttsuneda@yamanashi.ac.jp
Fuel Cell Nanomaterials Center, University of Yamanashi, Kofu 400-0021, Japan
- Takeshi Yamamoto
yamamoto@kuchem.kyoto-u.ac.jp
Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan
- Tatsuya Takagi
ttakagi@phs.osaka-u.ac.jp
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka, 565-0871, Japan
- Tayebeh Hosseini
tayebeh.hosseini@ gmail.com
Department of Chemistry, Faculty of Science, Alzahra University, Vanak, Tehran, Iran
- Terttu I. Hukka
terttu.hukka@tut.fi
Department of Chemistry and Bioengineering, Tampere University of Technology, P.O. Box 541, 33101, Tampere, Finland
- Thaciana Malaspina
thacianavmf@gmail.com
Instituto de Ciência e Tecnologia, Universidade Federal de São Paulo, 12231-280, São José dos Campos, São Paulo, Brazil
- Thomas Steinbrecher
thomas.steinbrecher@kit.edu
Inst. Phys. Chem., KIT, Kaiserstr. 12, 76131 Karlsruhe, Germany
- Tzu-Hao Chang
kevinchang@tmu.edu.tw
Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan
- Ulf Ryde
Ulf.Ryde@teokem.lu.se
Department of Theoretical Chemistry, Lund University, Chemical Centre, P.O. Box 124, SE-221 00 Lund, Sweden
- Viatcheslav V. Barkaline
barkaline@bntu.by
Belarusian National Technical University, Nezavisimosti ave., 65, Minsk, 220013, Belaru
- Victor L. Cruz
victor.cruz@iem.cfmac.csic.es
BIOPHYM, Macromolecular Physics Department, Instituto de Estructura de la Materia, CSIC, Serrano 113 bis, 28006, Madrid, Spain
- Walter Thiel
thiel@kofo.mpg.de
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470, Mülheim an der Ruhr, Germany
- Wei-Hsi Chen
whchen@iner.gov.tw
Graduate Institute of Biotechnology, National Taipei University of Technology, 1 Sec. 3 ZhongXiao E. Rd., Taipei, 10608, Taiwan
- Wei Jun Jin
wjjin@bnu.edu.cn
College of Chemistry, Beijing Normal University, Beijing, 100875, People's Republic of China
- Weihua Zhu
zhuwh@njust.edu.cn
Institute for Computation in Molecular and Materials Science and Department of Chemistry, Nanjing University of Science and Technology, Nanjing, 210094, China
- Wen-jing Shi, Jian-long Wang
wenjingfd@126.com
The Third Hospital of Shanxi Medical University, Taiyuan, 030053, China
- Wen-jing Shi
wenjingfd@126.com
The Third Hospital of Shanxi Medical University, Taiyuan, 030053, China
- Wen-jing Shi
wenjingfd@126.com
The Third Hospital of Shanxi Medical University, Taiyuan, 030053, China
- Wenjun Zheng
wjzheng@buffalo.edu
Physics Department, University at Buffalo, Buffalo, NY 14260
- Wilfred F. van Gunsteren
wfvgn@igc.phys.chem.ethz.ch
Laboratory of Physical Chemistry, Swiss Federal Institute of Technology, ETH, 8093 Zürich, Switzerland
- William W. Parson
parsonb@u.washington.edu
Department of Biochemistry, Structure and Design, University of Washington, Seattle, Washington 98195, United States
- Xavier Assfeld
Xavier.Assfeld@cbt.uhp-nancy.fr
Equipe de Chimie et Biochimie Théoriques, UMR 7565 CNRS UL, Université de Lorraine, BP 70239, 54506, Vandoeuvre-lès-Nancy, France
- Xianfu Lin
llc123@zju.edu.cn
Department of Chemistry, Zhejiang University, Hangzhou, 310027, People's Republic of China
- Xiao-Yu Kuang
scu_kuang@163.com
Institute of Atomic and Molecular Physics, Sichuan University, Chengdu, 610065, China
- Xiaojun Yao
xjyao@lzu.edu.cn
State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, China
- Xiaoqin Zou
zoux@missouri.edu
Department of Physics and Astronomy, University of Missouri, Columbia, Missouri 65211
- Xuming Deng
dengxm@jlu.edu.cn
Key Laboratory of Zoonosis, Ministry of Education, Institute of Zoonosis, College of Veterinary Medicine, Jilin University, Xi'an Road 5333, Changchun 130062, China
- Yan Zhang
yzhang2@vcu.edu
Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, 800 E. Leigh Street, P.O. Box
- Yanni Li
liyanni@tju.edu.cn
Key Laboratory of Systems Bioengineering, Ministry of Education, Department of Pharmaceutical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin, 300072, China
- Yeshitila Gebremichael
yeshig@wayne.edu
Department of Biomedical Engineering, Wayne State University, 818 W. Hancock St., Detroit, MI, 48201, USA
- Yi Xiao
Department of Physics, Biomolecular Physics and Modeling Group,

Huazhong University of Science
and Technology,
Wuhan, 430074, Hubei, China

YongQuan Wu
yqw@staff.shu.edu.cn
Shanghai Key Laboratory of
Modern
Metallurgy & Materials
Processing,
Shanghai University, YanChang
Road 149#,
ZhaBei District, Shanghai, 200072,
People's Republic of China

Yong Shen
cessy@mail.sysu.edu.cn
School of Chemistry and Chemical
Engineering,
Sun Yat-sen University, 510275,
Guangzhou, People's Republic of
China

Yongjun Liu
yongjunliu_1@sdu.edu.cn
School of Chemistry and Chemical
Engineering,
Shandong University, Jinan,
Shandong 250100, China

Youtao Song
youtaos@gmail.com
Province Key Laboratory of
Animal Resource and
Epidemic Disease Prevention,
College of Life Science, Liaoning
University,
Shenyang, 110036, China

Youyong Li
yyli@suda.edu.cn
Institute of Functional Nano & Soft
Materials (FUNSOM) and
Jiangsu Key Laboratory for
Carbon-Based Functional Materials
& Devices,
Soochow University, Suzhou,
Jiangsu 215123, China

Yovani Marrero-Ponce
yovanimp@uclv.edu.cu
Unit of Computer-Aided Molecular
"Biosilico"
Discovery and Bioinformatic
Research (CAMD-BIR Unit),
Faculty of Chemistry-Pharmacy,
Universidad Central "Martha
Abreu" de Las Villas,
Santa Clara, 54830, Villa Clara,
Cuba

Yufeng J. Tseng
yjtseng@csie.ntu.edu.tw
Graduate Institute of Biomedical
Electronics and Bioinformatics,
National Taiwan University, No.1
Sec.4,
Roosevelt Road, Taipei, Taiwan
106

Zahrabatoul Mosapour Kotena
zahrabatool2@siswa.um.edu.my
Chemistry Department, Faculty of
Science,
University of Malaya, 50603,
Kuala Lumpur, Malaysia

Zaida Luthey-Schulten
zan@illinois.edu
Department of Chemistry,
University of Illinois at Urbana-
Champaign,
Urbana, IL, 61801, USA

Zexing Cao
zxcao@xmu.edu.cn
State Key Laboratory of Physical
Chemistry of Solid Surfaces,
College of Chemistry and
Chemical Engineering,
Xiamen University, Xiamen
360015, China

Zhi-ming Li
zmli@fudan.edu.cn
Department of Chemistry,
Fudan University, Shanghai,
200433, People's Republic of
China

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Editor:

R.Mutyala.
MMCC Results
RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.
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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Exploring Molecular Insights into Aggregation of Hydrotrope Sodium Cumene Sulfonate in Aqueous Solution: A Molecular Dynamics Simulation Study

Shubhadip Das, Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **119**, 3142–3154, 2015.

Hydrotropes are an important class of molecules that enhance the solubility of an otherwise insoluble or sparingly soluble solute in water. Besides this, hydrotropes are also known to self-assemble in aqueous solution and form aggregates. It is the hydrotrope aggregate that helps in solubilizing a solute molecule in water. In view of this, we try to understand the underlying mechanism of self-aggregation of hydrotrope sodium cumene sulfonate (SCS) in water. We have carried out classical molecular dynamics simulations of aqueous SCS solutions with a regime of concentrations.

Single Chain Structure of a Poly(N-isopropylacrylamide) Surfactant in Water

Lauren J. Abbott, Ashley K. Tucker, Mark J. Stevens [Sandia National Laboratories]

J. Phys. Chem. B., **119**, 3837–3845, 2015.

We present atomistic simulations of a single PNIPAM–alkyl copolymer surfactant in aqueous solution at temperatures below and above the LCST of PNIPAM. We compare properties of the surfactant with pure PNIPAM oligomers of similar lengths, such as the radius of gyration and solvent accessible surface area, to determine the differences in their structures and transition behavior. We also explore changes in polymer–polymer and polymer–water interactions, including hydrogen bond formation. The expected behavior is observed in the pure PNIPAM oligomers, where the backbone folds onto itself above the LCST in order to shield the hydrophobic groups from water.



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8013 Los Sabalos Street
San Diego, CA 92126
Tel. (858) 663-0162
e-mail: mmccresults@gmail.com

Dr. R. Mutyala.
RR Labs Inc., 8013 Los Sabalos St.
San Diego, CA 92126
Editors Emeritus: Bruce Gelin, Ph.D.
David Busath, M.D.

Dr. Gelin was founder of MMCC Results and edited volumes 1-6.
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Assistant Editors:

Sowmya .N
Rational Labs, Hyderabad., India

Sambasivareddy M
RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design

Discovery of biphenyl-based VEGFR-2 inhibitors. Part 3: Design, synthesis and 3D-QSAR studies

Wen Lu, Pengfei Li, Yuanyuan Shan, Ping Su, Jinfeng Wang, Yaling Shi, Jie Zhang [Xi'an Jiaotong University]

Bioorg. and Med.Chem., **23**, 1044-1054 ,2015.

VEGFR-2 plays an essential role in angiogenesis and is a central target for anticancer drug discovery. In order to develop novel VEGFR-2 inhibitors, we designed and synthesized 33 biphenyl amides based on our previously reported lead compound. The biological results indicated that four compounds (**18b**, **20e**, **20h** and **20j**) are potent VEGFR-2 inhibitors which are comparable to positive control. Compound **18b** displayed the most potent VEGFR-2 inhibition with IC₅₀ value of 2.02 nM. Moreover, it exhibited promising antiproliferative activity against MCF-7 and SMMC-7721 cells with IC₅₀ values of 1.47 μM and 5.98 μM, respectively.

Dissipative particle dynamics study on self-assembled platycodin structures: The potential biocarriers for drug delivery

Xingxing Dai, Haiou Ding, Qianqian Yin, Guang Wan, Xinyuan Shi [Beijing University of Chinese Medicine], Yanjiang Qiao

J. Mol.Graph. and Mod., **57**, 20-26,2015.

Platycodin, as a kind of plant based biosurfactants, are saponins which derived from the root of *Platycodon grandiflorum* A. DC. It has been confirmed that platycodin have the potential to enhance the solubility of hydrophobic drugs and function as the drug carrier, which depends on their micellization over critical micelle concentration (CMC) in aqueous solutions. With the purpose of investigating the effects of influencing factors on the micellization behavior of platycodin and obtaining the phase behavior details at a mesoscopic level, dissipative particle dynamics (DPD) simulations method has been adopted in this study.

Can structural features of kinase receptors provide clues on selectivity and inhibition? A molecular modeling study

Sarangan Ravichandran [Frederick National Laboratory for Cancer Research (FNLCR)], Brian T. Luke, Jack R. Collins

J. Mol.Graph. and Mod., **57**, 36-48,2015.

Cancer is a complex disease resulting from the uncontrolled proliferation of cell signaling events. Protein kinases have been identified as central molecules that participate overwhelmingly in oncogenic events, thus becoming key targets for anticancer drugs. A majority of studies converged on the idea that ligand-binding pockets of kinases retain clues to the inhibiting abilities and cross-reacting tendencies of inhibitor drugs. Even though these ideas are critical for drug discovery, validating them using experiments is not only difficult, but also in some cases infeasible. To overcome these limitations and to test these ideas at the molecular level, we present here the results of receptor-focused in-silico docking of nine MARKETED drugs to 19 different wild-type and mutated kinases chosen from a wide range of families.

Medicinal Chemistry and Drug Design (Cont'd)

Homology modeling and molecular dynamics simulation of N-myristoyltransferase from *Plasmodium falciparum*: an insight into novel antimalarial drug design

Paulomi Paul, Abhishek Chowdhury [Assam University],
Anupam Das Talukdar, Manabendra Dutta Choudhury

J. Mol.Mod., **21**, 37, 2015.

Malaria is an infectious disease caused by parasites of the genus *Plasmodium*. It leads to approximately 1 million deaths per annum worldwide, with an increase number of 6.27 million deaths in 2012 alone. Validation of new antimalarial targets is very important in the context of the rise in resistance to current drugs. One such putative target is the enzyme N-myristoyltransferase (NMT), which catalyzes the attachment of the fatty acid myristate to protein substrates (N-myristoylation) for activation. Reports suggests that NMT is an essential and chemically docile target in malaria parasites both in vitro and in vivo, and the selective inhibition of N-myristoylation leads to irreversible failure to form an inner membrane complex—an essential subcellular organelle in the parasite life cycle.

Rational design of biaryl pharmacophore inserted nescapine derivatives as potent tubulin binding anticancer agents

Seneha Santoshi, Naresh Kumar Manchukonda, Charu Suri, Manya Sharma, Balasubramanian Sridhar, Silja Joseph, Manu Lopus, Srinivas Kantevari, Iswar Baitharu, Pradeep Kumar Naik [Jaypee University of Information Technology]

J.Comp.Aided. Mol.des. **29**, 249-270 , 2015.

We have strategically designed a series of nescapine derivatives by inserting biaryl pharmacophore (a major structural constituent of many of the microtubule-targeting natural anticancer compounds) onto the scaffold structure of nescapine. Molecular interaction of these derivatives with α,β -tubulin heterodimer was investigated by molecular docking, molecular dynamics simulation, and binding free energy calculation. The predictive binding affinity indicates that the newly designed nescapinoids bind to tubulin with a greater affinity.

Atomic-Level Study of the Effects of O4 Molecules on the Structural Properties of Protofibrillar A β Trimer: β -Sheet Stabilization, Salt Bridge Protection, and Binding Mechanism

Yunxiang Sun, Wenhui Xi, Guanghong Wei [Fudan University]

J. Phys. Chem. B., **119**, 2786–2794, 2015.

Alzheimer's disease (AD) is associated with the aggregation of amyloid- β (A β) peptides into toxic prefibrillar aggregates. Recent experiments reported that small organic molecule O4 decreases the concentration of toxic oligomers by promoting fibrillation and thus reduces A β toxicity. However, the atomic-level details of O4–A β -oligomer interaction are largely unknown. In this work, we studied the structural stability of the fibrillike A β (17–42) trimer by performing atomistic molecular dynamics simulations of 1.5 μ s in total on the trimer with and without O4. We found that the A β (17–42) trimer is unstable without O4, whereas its structural stability is greatly enhanced with O4. Four binding sites were found around residues F20, S26, and M35, namely the central hydrophobic core (CHC) site, the turn site, and two hydrophobic-groove sites.

Medicinal Chemistry and Drug Design (Cont'd)

Systematic Drug Repositioning for a Wide Range of Diseases with Integrative Analyses of Phenotypic and Molecular Data

Hiroaki Iwata, Ryusuke Sawada, Sayaka Mizutani, Yoshihiro Yamanishi [Kyushu University]

J.Chem. Infor. and Mod. **55**, 446–459, 2015.

Drug repositioning, or the application of known drugs to new indications, is a challenging issue in pharmaceutical science. In this study, we developed a new computational method to predict unknown drug indications for systematic drug repositioning in a framework of supervised network inference. We defined a descriptor for each drug–disease pair based on the phenotypic features of drugs (e.g., medicinal effects and side effects) and various molecular features of diseases (e.g., disease-causing genes, diagnostic markers, disease-related pathways, and environmental factors) and constructed a statistical model to predict new drug–disease associations for a wide range of diseases in the International Classification of Diseases.

A Refined Model of the HCV NS5A Protein Bound to Daclatasvir Explains Drug-Resistant Mutations and Activity against Divergent Genotypes

Khaled H. Barakat [University of Alberta], Anwar Anwar-Mohamed, Jack A. Tuszyński, Morris J. Robins, D. Lorne Tyrrell, Michael Houghton

J.Chem. Infor. and Mod. **55**, 362–373, 2015.

Many direct-acting antiviral agents (DAAs) that selectively block hepatitis C virus (HCV) replication are currently under development. Among these agents is Daclatasvir, a first-in-class inhibitor targeting the NS5A viral protein. Although Daclatasvir is the most potent HCV antiviral molecule yet developed, its binding location and mode of binding remain unknown. The drug exhibits a low barrier to resistance mutations, particularly in genotype 1 viruses, but its efficacy against other genotypes is unclear. Using state-of-the-art modeling techniques combined with the massive computational power of Blue Gene/Q, we identified the atomic interactions of Daclatasvir within NS5A for different HCV genotypes and for several reported resistant mutations.

A Virtual Screening Approach For Identifying Plants with Anti H5N1 Neuraminidase Activity

Nur Kusaira Khairul Ikram, Jacob D. Durrant, Muchtaridi Muchtaridi, Ayunni Salihah Zalaludin, Neny Purwitasari, Nornisah Mohamed, Aisyah Saad Abdul Rahim, Chan Kit Lam, Yahaya M. Normi, Noorsaadah Abd Rahman, Rommie E. Amaro, Habibah A Wahab [Universiti Sains Malaysia]

J.Chem. Infor. and Mod. **55**, 308–316, 2015.

Recent outbreaks of highly pathogenic and occasional drug-resistant influenza strains have highlighted the need to develop novel anti-influenza therapeutics. Here, we report computational and experimental efforts to identify influenza neuraminidase inhibitors from among the 3000 natural compounds in the Malaysian-Plants Natural-Product (NADI) database. These 3000 compounds were first docked into the neuraminidase active site. The five plants with the largest number of top predicted ligands were selected for experimental evaluation. Twelve specific compounds isolated from these five plants were shown to inhibit neuraminidase, including two compounds with IC₅₀ values less than 92 μ M.

Medicinal Chemistry and Drug Design (Cont'd)

Molecular Structure and Pronounced Conformational Flexibility of Doxorubicin in Free and Conjugated State within a Drug–Peptide Compound

Yana Tsoneva, Hendrik R. A. Jonker, Manfred Wagner, Alia Tadjer, Marco Lelle, Kalina Peneva, Anela Ivanova[University of Sofia, Faculty of Chemistry and Pharmacy]

J. Phys. Chem. B., **119**, 3001–3013, 2015.

The search for targeted drug delivery systems requires the design of drug–carrier complexes, which could both reach the malignant cells and preserve the therapeutic substance activity. A promising strategy aimed at enhancing the uptake and reducing the systemic toxicity is to bind covalently the drug to a cell-penetrating peptide. To understand the structure–activity relationship in such preparations, the chemotherapeutic drug doxorubicin was investigated by unrestrained molecular dynamics simulations, supported by NMR, which yielded its molecular geometry in aqueous environment. Furthermore, the structure and dynamics of a conjugate of the drug with a cell-penetrating peptide was obtained from molecular dynamics simulations in aqueous solution.

Reduction of Urease Activity by Interaction with the Flap Covering the Active Site

Lee Macomber, Mona S. Minkara, Robert P. Hausinger, Kenneth M. Merz, Jr. [Michigan State University]

J.Chem. Infor. and Mod. **55**, 354–361, 2015.

With the increasing appreciation for the human microbiome coupled with the global rise of antibiotic resistant organisms, it is imperative that new methods be developed to specifically target pathogens. To that end, a novel computational approach was devised to identify compounds that reduce the activity of urease, a medically important enzyme of *Helicobacter pylori*, *Proteus mirabilis*, and many other microorganisms. Urease contains a flexible loop that covers its active site; Glide was used to identify small molecules predicted to lock this loop in an open conformation.

Discovery of Small Molecule CD40–TRAF6 Inhibitors

Barbara Zarzycka, Tom Seijkens, Sander B. Nabuurs, Tina Ritschel, Jochen Grommes, Oliver Soehnlein, Roy Schrijver, Claudia M. van Tiel, Tilman M. Hackeng, Christian Weber, Fabian Giehler, Arnd Kieser, Esther Lutgens, Gert Vriend, Gerry A. F. Nicolaes [Maastricht University]

J.Chem. Infor. and Mod. **55**, 294–307, 2015.

The CD154–CD40 receptor complex plays a pivotal role in several inflammatory pathways. Attempts to inhibit the formation of this complex have resulted in systemic side effects. Downstream inhibition of the CD40 signaling pathway therefore seems a better way to ameliorate inflammatory disease. To relay a signal, the CD40 receptor recruits adapter proteins called tumor necrosis factor receptor-associated factors (TRAFs). CD40–TRAF6 interactions are known to play an essential role in several inflammatory diseases. We used *in silico*, *in vitro*, and *in vivo* experiments to identify and characterize compounds that block CD40–TRAF6 interactions.

Quantitative Structure-Activity Relations

Benefits of statistical molecular design, covariance analysis, and reference models in QSAR: a case study on acetylcholinesterase

C. David Andersson, J. Mikael Hillgren, Cecilia Lindgren, Weixing Qian, Christine Akfur, Lotta Berg, Fredrik Ekström, Anna Linusson[Umeå University]

J.Comp.Aided. Mol.des. **29**, 199-215 , 2015.

Scientific disciplines such as medicinal- and environmental chemistry, pharmacology, and toxicology deal with the questions related to the effects small organic compounds exert on biological targets and the compounds' physicochemical properties responsible for these effects. A common strategy in this endeavor is to establish structure-activity relationships (SARs). A common strategy in this endeavor is to establish structure-activity relationships (SARs). The aim of this work was to illustrate benefits of performing a statistical molecular design (SMD) and proper statistical analysis of the molecules' properties before SAR and quantitative structure-activity relationship (QSAR) analysis.

eCounterscreening: Using QSAR Predictions to Prioritize Testing for Off-Target Activities and Setting the Balance between Benefit and Risk

Robert P. Sheridan [Merck Research Laboratories], Daniel R. McMaster, Johannes H. Voigt, Mary Jo Wildey

J.Chem. Infor. and Mod. **55**, 231-238, 2015.

During drug development, compounds are tested against counterscreens, a panel of off-target activities that would be undesirable for a drug to have. Testing every compound against every counterscreen is generally too costly in terms of time and MONEY , and we need to find a rational way of prioritizing counterscreen testing. Here we present the eCounterscreening paradigm, wherein predictions from QSAR models for counterscreen activity are used to generate a recommendation as to whether a specific compound in a specific project should be tested against a specific counterscreen.

Host-Guest Systems

Theoretical prediction of the host-guest interactions between novel photoresponsive nanorings and C60: A strategy for facile encapsulation and release of fullerene

Kun Yuan, Jing-Shuang Dang, Yi-Jun Guo , Xiang Zhao [Xi'an Jiaotong University]

J. Comp. Chem., **36**, 518-528, 2015.

A series of photoresponsive-group-containing nanorings hosts with 12~14 Å in diameter is designed by introducing different number of azo groups as the structural composition units. And the host-guest interactions between fullerene C60 and those nanoring hosts were investigated theoretically at M06-2X/6-31G(d)//M06-L/MIDI! and wB97X-D/6-31G(d) levels. Analysis on geometrical characteristics and host-guest binding energies revealed that the designed nanoring molecule (labeled as 7) which is composed by seven azo groups and seven phenyls is the most feasible host for encapsulation of C60 guest among all candidates.

Carbon Nanoparticles

Removal of trihalomethanes from aqueous solution through armchair carbon nanotubes: A molecular dynamics study

Jafar Azamat, Alireza Khataee [University of Tabriz], Sang Woo Joo, Binfeng Yin

J. Mol.Graph. and Mod., **57**, 70-75,2015.

Molecular dynamics simulations were performed to investigate the removal of trihalomethanes (THMs) including CH₃Cl, CH₂Cl₂ and CHCl₃ from aqueous solutions by armchair carbon nanotubes (CNTs) under induced pressure. The studied system involved the armchair CNTs embedded between two graphene sheets with an aqueous solution of THMs in the simulation box. An external pressure was applied to the system along the z-axis of the simulation box. Six types of armchair CNTs with different diameter were used in this work, included (4,4), (5,5), (6,6), (7,7), (8,8) and (9,9) CNTs.

H₂ adsorption on Ag-nanocluster/single-walled carbon nanotube composites: A molecular dynamics study on the effects of nanocluster size, diameter, and chirality of nanotube

Hamed Akbarzadeh [Hakim Sabzevari University], Amir Nasser Shamkhali

J. Comp. Chem., **36**, 433–440, 2015.

The H₂ physisorption on AgN (with N = 32, 108, 256, 500, and 864)/carbon nanotube (CNT; in armchair and zigzag structures with diameters between 0.54 and 2.98 nm) composites were studied by molecular dynamic simulation to investigate the effect of nanocluster size, diameter, and chirality of nanotube on the adsorption phenomena. The calculations indicate that the effects of nanocluster properties are more important than those of the nanotube, in such a way that increase of nanocluster size, decreases the H₂ adsorption. Also, the diameter and chirality of CNTs have considerable influence on the adsorption phenomena.

1.2. Biopolymers

Bioinformatics and Cheminformatics

LIGSIFT: an open-source tool for ligand structural alignment and virtual screening

Amrith Roy, Jeffrey Skolnick [Georgia Institute of Technology]

Bioinformatics. **31**, 539-544, 2015.

Shape-based alignment of small molecules is a widely used approach in computer-aided drug discovery. Most shape-based ligand structure alignment applications, both commercial and freely available ones, use the Tanimoto coefficient or similar functions for evaluating molecular similarity. Major drawbacks of using such functions are the size dependence of the score and the fact that the statistical significance of the molecular match using such metrics is not reported. We describe a new open-source ligand structure alignment and virtual screening (VS) algorithm, LIGSIFT, that uses Gaussian molecular shape overlay for fast small molecule alignment and a size-independent scoring function for efficient VS based on the statistical significance of the score.

Bioinformatics and Cheminformatics (Cont'd)

IntSide: a web server for the chemical and biological examination of drug side effects

Ryan Taylor [Brigham Young University] , Ryan H. Miller, Ryan D. Miller, Michael Porter, James Dalglish ,John T. Prince

Bioinformatics. **31**, 612-613, 2015.

Modern lipidomics is largely dependent upon structural ontologies because of the great diversity exhibited in the lipidome, but no automated lipid classification exists to facilitate this partitioning. The size of the putative lipidome far exceeds the number currently classified, despite a decade of work. Automated classification would benefit ongoing classification efforts by decreasing the time needed and increasing the accuracy of classification while providing classifications for mass spectral identification algorithms. We introduce a tool that automates classification into the LIPID MAPS ontology of known lipids with >95% accuracy and novel lipids with 63% accuracy.

WebPSN: a web server for high-throughput investigation of structural communication in biomacromolecules

Michele Seeber, Angelo Felling, Francesco Raimondi, Simona Mariani, Francesca Fanelli [University of Modena and Reggio Emilia]

Bioinformatics. **31**, 779-781, 2015.

We developed a mixed Protein Structure Network (PSN) and Elastic Network Model-Normal Mode Analysis (ENM-NMA)-based strategy (i.e. PSN-ENM) to investigate structural communication in biomacromolecules. The approach starts from a Protein Structure Graph and searches for all shortest communication pathways between user-specified residues. The graph is computed on a single preferably high-resolution structure. Information on system's dynamics is supplied by ENM-NMA. The PSN-ENM methodology is made of multiple steps both in the setup and analysis stages, which may discourage inexperienced users.

STOCK: Structure mapper and online coarse-graining kit for molecular simulations

Staš Bevc [National Institute of Chemistry, Ljubljana], Christoph Junghans , Matej Praprotnik

J. Comp. Chem., **36**, 467-477, 2015.

We present a web toolkit SStructure mapper and Online Coarse-graining Kit for setting up coarse-grained molecular simulations. The kit consists of two tools: structure mapping and Boltzmann inversion tools. The aim of the first tool is to define a molecular mapping from high, for example, all-atom, to low, that is, coarse-grained, resolution. Using a graphical user interface it generates input files, which are compatible with standard coarse-graining packages, for example, Versatile Object-oriented Toolkit for Coarse-graining Applications and DL_CGMAP.

Etomica: An object-oriented framework for molecular simulation

Andrew J. Schultz , David A. Kofke [The State University of New York]

J. Comp. Chem., **36**, 573-583, 2015.

We describe the design of an object-oriented library of software components that are suitable for constructing simulations of systems of interacting particles. The emphasis of the discussion is on the general design of the components and how they interact, and less on details of the programming interface or its implementation. Example code is provided as an aid to understanding object-oriented programming structures and to demonstrate how the framework is applied.

Bioinformatics and Cheminformatics (Cont'd)

Toward a Benchmarking Data Set Able to Evaluate Ligand- and Structure-based Virtual Screening Using Public HTS Data

Martin Lindh, Fredrik Svensson, Wesley Schaal, Jin Zhang, Christian Sköld, Peter Brandt, Anders Karlén [Uppsala University]

J.Chem. Infor. and Mod. **55**, 343–353, 2015.

Virtual screening has the potential to accelerate and reduce costs of probe development and drug discovery. To develop and benchmark virtual screening methods, validation data sets are commonly used. Over the years, such data sets have been constructed to overcome the problems of analogue bias and artificial enrichment. With the rapid growth of public domain databases containing high-throughput screening data, such as the PubChem BioAssay database, there is an increased possibility to use such data for validation. In this study, we identify PubChem data sets suitable for validation of both structure- and ligand-based virtual screening methods.

DOCKTITE—A Highly Versatile Step-by-Step Workflow for Covalent Docking and Virtual Screening in the Molecular Operating Environment

Christoph Scholz, Sabine Knorr, Kay Hamacher, Boris Schmidt [Technische Universität Darmstadt]

J.Chem. Infor. and Mod. **55**, 398–406, 2015.

The formation of a covalent bond with the target is essential for a number of successful drugs, yet tools for covalent docking without significant restrictions regarding warhead or receptor classes are rare and limited in use. In this work we present DOCKTITE, a highly versatile workflow for covalent docking in the Molecular Operating Environment (MOE) combining automated warhead screening, nucleophilic side chain attachment, pharmacophore-based docking, and a novel consensus scoring approach.

Pharmacophore Modeling Using Site-Identification by Ligand Competitive Saturation (SILCS) with Multiple Probe Molecules

Wenbo Yu, Sirish Kaushik Lakkaraju, E. Prabhu Raman, Lei Fang, Alexander D. MacKerell, Jr. [University of Maryland]

J.Chem. Infor. and Mod. **55**, 407–420, 2015.

Receptor-based pharmacophore modeling is an efficient computer-aided drug design technique that uses the structure of the target protein to identify novel LEADS. The Site-Identification by Ligand Competitive Saturation (SILCS) assisted pharmacophore modeling protocol (SILCS-Pharm) was introduced recently to address these issues, as SILCS naturally takes both protein flexibility and desolvation effects into account by using full molecular dynamics simulations to determine 3D maps of the functional group-affinity patterns on a target receptor. In the present work, the SILCS-Pharm protocol is extended to use a wider range of probe molecules including benzene, propane, methanol, formamide, acetaldehyde, methylammonium, acetate and water.

Protein Secondary Structure

Probing the Unfolded Configurations of a β -Hairpin Using Sketch-Map

Albert Ardevol [USI-Campus], Gareth A. Tribello, Michele Ceriotti, Michele Parrinello

J. Chem. Theor. and Comp. **11**, 1086–1093, 2015.

This work examines the conformational ensemble involved in β -hairpin folding by means of advanced molecular dynamics simulations and dimensionality reduction. A fully atomistic description of the protein and the surrounding solvent molecules is used, and this complex energy landscape is sampled by means of parallel tempering metadynamics simulations. The ensemble of configurations explored is analyzed using the recently proposed sketch-map algorithm.

Protein Secondary Structure (Cont'd)

Folding or Misfolding: The Choice of β -Hairpin

Qiang Shao [Chinese Academy of Sciences]

J. Phys. Chem. B., **119**, 3893–3900, 2015.

Proteins fold through complex inter-residue interactions which are mutually supportive and cooperatively lead to thermodynamically favorable native structures. Competing (misfolded) structures, however, could exist, which might affect the thermodynamic and kinetic properties of folded structure. Running long-time REMD simulations on two β -structured polypeptides, the present study identifies the folded and (less populated) competing misfolded states of β -hairpins. Of particular interest is a one-residue shifted misfolded state which has been often seen in previous reports.

Comparative or Homology Modeling

Molecular modeling and docking study on dopamine D2-like and serotonin 5-HT_{2A} receptors

Xinli Duan, Min Zhang, Xin Zhang, Fang Wang, Ming Lei [Beijing University of Chemical Technology]

J. Mol. Graph. and Mod., **57**, 143-155, 2015.

Psychiatric disorders, such as schizophrenia, bipolar disorder and major depression, are paid more and more attention by human due to their upward tendency in modern society. D2-like and 5-HT_{2A} receptors have been proposed as targets of antipsychotic drugs. Atypical antipsychotic drugs have been deemed to improve the treatment of positive, negative and extrapyramidal symptoms. Accordingly, homology models of dopamine D₂, D₃, D₄ and serotonin 5-HT_{2A} receptors have been built on the high-resolution crystal structure of the β_2 -adrenergic receptor, and refined by molecular dynamics simulations.

Structural prediction of a novel laminarinase from the psychrophilic *Glaciozyma antarctica* PI12 and its temperature adaptation analysis

Sepideh Parvizpour [Universiti Teknologi Malaysia], Jafar Razmara, Ashraf Fadhil Jomah, Mohd Shahir Shamsir, Rosli Mohd Illias

J. Mol. Mod., **21**, 63, 2015.

Here, we present a novel psychrophilic β -glucanase from *Glaciozyma antarctica* PI12 yeast that has been structurally modeled and analyzed in detail. To our knowledge, this is the first attempt to model a psychrophilic laminarinase from yeast. Because of the low sequence identity (<40 %), a threading method was applied to predict a 3D structure of the enzyme using the MODELLER9v12 program. The results of a comparative study using other mesophilic, thermophilic, and hyperthermophilic laminarinases indicated several amino acid substitutions on the surface of psychrophilic laminarinase that totally increased the flexibility of its structure for efficient catalytic reactions at low temperatures.

Protein Conformational Analysis

Speed of Conformational Change: Comparing Explicit and Implicit Solvent Molecular Dynamics Simulations

Ramu Anandakrishnan, Aleksander Drozdetski, Ross C. Walker, Alexey V. Onufriev [Virginia Tech]

Biophysical Journal. **108**, 1153-1164, 2015.

Adequate sampling of conformation space remains challenging in atomistic simulations, especially if the solvent is treated explicitly. Implicit-solvent simulations can speed up conformational sampling significantly. We compare the speed of conformational sampling between two commonly used methods of each class: the explicit-solvent particle mesh Ewald (PME) with TIP3P water model and a popular generalized Born (GB) implicit-solvent model, as implemented in the AMBER package. We systematically investigate small (dihedral angle flips in a protein), large (nucleosome tail collapse and DNA unwrapping), and mixed (folding of a miniprotein) conformational changes, with nominal simulation times ranging from nanoseconds to microseconds depending on system size.

Agonist binding by the β 2-adrenergic receptor: an effect of receptor conformation on ligand association–dissociation characteristics

Anita Plazinska, Wojciech Plazinski [Polish Academy of Sciences], Krzysztof Jozwiak

Eur.Biophys., **44**, 149-163 ,2015.

The β 2-adrenergic receptor (β 2-AR), a G protein-coupled receptor (GPCR), is a physiologically important transmembrane protein that is a target for drugs used for treatment of asthma and cardiovascular diseases. Study of the first steps of ligand recognition and the molecular basis of ligand binding to the orthosteric site is essential for understanding the pharmacological properties of the receptor. In this work we investigated the characteristic features of the agonist association–dissociation process to and from the different conformational forms of β 2-AR by use of advanced molecular modeling techniques.

Self-Binding Peptides: Folding or Binding?

Chao Yang, Shilei Zhang, Ping He, Congcong Wang, Jian Huang, Peng Zhou [University of Electronic Science and Technology of China (UESTC)]

J.Chem. Infor. and Mod. **55**, 329–342, 2015.

Self-binding peptides (SBPs) represent those short peptide segments within monomeric proteins to fulfill their biological functions by dynamically binding to/unbinding from their target domains in the same monomers. They are frequently found in disordered or unstructured regions of proteins that are now known to be not simply helices, loops, or linkers and adopt a well-defined structure upon binding. In this study, we systematically explored the structural basis, energy landscape, and thermodynamic properties of SBP-mediated biological mechanisms by dissecting dynamic interactions of SBPs with their cognate targets.

Evolutionary Conserved Tyr169 Stabilizes the β 2- α 2 Loop of the Prion Protein

Danzhi Huang , Amedeo Caflisch [University of Zürich]

J. Am. Chem. Soc., **137**, 2948–2957, 2015.

Experimental evidence indicates that the primary structure of the β 2- α 2 loop region (residues 165–175) in mammalian prion proteins (PrP) influences the conversion from the cellular species (PrP^C) to the β -sheet-rich aggregate. Here, we captured the transition of the β 2- α 2 loop from 310-helical turn to β turn by unbiased molecular dynamics simulations of the single-point mutant Y169G. Multiple conformations along the spontaneous transition of the mutant were then used as starting point for sampling of the free-energy surface of the wild type and other single-point mutants.

Protein Conformational Analysis (Cont'd)

Studies of conformational changes of an arginine-binding protein from *Thermotoga maritima* in the presence and absence of ligand via molecular dynamics simulations with the coarse-grained UNRES force field

Agnieszka G. Lipska, Adam K. Sieradzan, Paweł Krupa, Magdalena A. Mozolewska, Sabato D'Auria, Adam Liwo [University of Gdansk]

J. Mol.Mod., **21**, 64, 2015.

The arginine-binding protein (ArgBP) from the hyperthermophilic eubacterium *Thermotoga maritima* (TmArgBP) is responsible for arginine transport through the bacterial cell membrane. The protein binds a single molecule of L-arginine, which results in conformational changes due to hinge bending. Thereby, TmArgBP acquires one of two possible conformations: open (without the presence of the arginine ligand) and closed (in the presence of the arginine ligand). Here we report a molecular dynamics study of the influence of the presence or absence of the ligand on the dynamics of TmArgBP, using the coarse-grained UNRES force field.

Independent Metrics for Protein Backbone and Side-Chain Flexibility: Time Scales and Effects of Ligand Binding

Julian E. Fuchs, Birgit J. Waldner, Roland G. Huber, Susanne von Grafenstein, Christian Kramer, Klaus R. Liedl [University of Innsbruck]

J. Chem. Theor. and Comp., **11**, 851–860, 2015.

Conformational dynamics are central for understanding biomolecular structure and function, since biological macromolecules are flexible at room temperature and in solution. Computational methods are nowadays capable of providing valuable information on the conformational ensembles of biomolecules. However, analysis tools and intuitive metrics that capture dynamic information from in silico generated structural ensembles are limited. We present a novel approach for capturing positional fluctuations based on multiple local alignments instead of one single global alignment.

High-Resolution Coarse-Grained Modeling Using Oriented Coarse-Grained Sites

Thomas K. Haxton [Lawrence Berkeley National Laboratory]

J. Chem. Theor. and Comp., **11**, 1244–1254, 2015.

We introduce a method to bring nearly atomistic resolution to coarse-grained models, and we apply the method to proteins. Using a small number of coarse-grained sites (about one per eight atoms) but assigning an independent three-dimensional orientation to each site, we preferentially integrate out stiff degrees of freedom (bond lengths and angles, as well as dihedral angles in rings) that are accurately approximated by their average values, while retaining soft degrees of freedom (unconstrained dihedral angles) mostly responsible for conformational variability.

Molecular Dynamics Simulations of 441 Two-Residue Peptides in Aqueous Solution: Conformational Preferences and Neighboring Residue Effects with the Amber ff99SB-ildn-NMR Force Field

Shuxiang Li, Casey T. Andrews, Tamara Frembgen-Kesner, Mark S. Miller, Stephen L. Siemonsma, Timothy D. Collingsworth, Isaac T. Rockafellow, Nguyet Anh Ngo, Brady A. Campbell, Reid F. Brown, Chengxuan Guo, Michael Schrodt, Yu-Tsan Liu, Adrian H. Elcock [University of Iowa]

J. Chem. Theor. and Comp., **11**, 1315–1329, 2015.

Understanding the intrinsic conformational preferences of amino acids and the extent to which they are modulated by neighboring residues is a key issue for developing predictive models of protein folding and stability. Here we present the results of 441 independent explicit-solvent MD simulations of all possible two-residue peptides that contain the 20 standard amino acids with histidine modeled in both its neutral and protonated states. $^3J_{\text{HNH}\alpha}$ coupling constants and $\delta\text{H}\alpha$ chemical shifts calculated from the MD simulations correlate quite well with recently published experimental measurements for a corresponding set of two-residue peptides.

Protein Structure Analysis

Prediction of the structures of helical membrane proteins based on a minimum unfavorable contacts approach

Siladitya Padhi, Siddabattula Ramakrishna, U. Deva Priyakumar [International Institute of Information Technology, Hyderabad]

J. Comp. Chem., **36**, 539–552, 2015.

An understanding of structure–function relationships of membrane proteins continues to be a challenging problem, owing to the difficulty in obtaining their structures experimentally. This study suggests a method for modeling membrane protein structures that can be used to generate a reliable initial conformation prior to the use of other approaches for sampling conformations. It involves optimizing the orientation of hydrophilic residues so as to minimize unfavorable contacts with the hydrophobic tails of the lipid bilayer.

Protein Dynamics

Capsaicin inhibits collagen fibril formation and increases the stability of collagen fibers

Sathiamurthi Perumal, Kriti Dubey, Rahul Badhwar, Kodimattan Joseph George, Rakesh Kumar Sharma, Ganesh Bagler, Balaraman Madhan, Karunakar Kar [Indian Institute of Technology Jodhpur]

Eur. Biophys., **44**, 69–76, 2015.

Capsaicin is a versatile plant product which has been ascribed several health benefits and anti-inflammatory and analgesic properties. We have investigated the effect of capsaicin on the molecular stability, self-assembly, and fibril stability of type-I collagen. It was found that capsaicin suppresses collagen fibril formation, increases the stability of collagen fibers in tendons, and has no effect on the molecular stability of collagen. Turbidity assay data show that capsaicin does not promote disassembly of collagen fibrils. However, capsaicin moderately protects collagen fibrils from enzymatic degradation.

Inter-domain helix h10DOMI–h1DOMII is important in the molecular interaction of bovine serum albumin with curcumin: spectroscopic and computational analysis

Dhakaram Pangei, Charu Kapil, Mohamad Aman Jairajpuri, Priyanka Sen [Utkal University]

Eur. Biophys., **44**, 139–148, 2015.

The importance of domain II in the molecular interaction of bovine serum albumin (BSA) with curcumin was investigated by fluorescence spectroscopy and molecular docking. At pH 7.4 BSA is in its native state. Domain III of BSA unfolds at pH 4.0, and domains I and III unfold in the presence of 5 M urea. Curcumin has a high quenching constant ($K_{SV} \sim 104 \text{ M}^{-1}$) and moderate binding affinity ($n \sim 0.5$). The standard free energy change ($\Delta G^\circ \sim -25 \text{ kJ mol}^{-1}$) indicates that binding is spontaneous. No significant change in ΔG° observed after unfolding of domain I or domain III.

Essential dynamics for the study of microstructures in liquids

Maira D'Alessandro, Andrea Amadei, Mauro Stener, Massimiliano Aschi [Universita' di l'Aquila]

J. Comp. Chem., **36**, 399–407, 2015.

Essential Dynamics (ED) is a powerful tool for analyzing molecular dynamics (MD) simulations and it is widely adopted for conformational analysis of large molecular systems such as, for example, proteins and nucleic acids. In this study, we extend the use of ED to the study of clusters of arbitrary size constituted by weakly interacting particles, for example, atomic clusters and supramolecular systems. The key feature of the method we present is the identification of the relevant atomic-molecular clusters to be analyzed by ED for extracting the information of interest.

Protein Dynamics (Cont'd)

Activation of Corticotropin-Releasing Factor 1 Receptor: Insights from Molecular Dynamics Simulations

Rajesh Singh, Navjeet Ahalawat, Rajesh K. Murarka [Indian Institute of Science Education and Research Bhopal]

J. Phys. Chem. B., **119**, 2806–2817, 2015.

G-protein-coupled receptors (GPCRs) constitute the largest family of membrane-bound proteins involved in translation of extracellular signals into intracellular responses. They regulate diverse physiological and pathophysiological processes, and hence, they are prime drug targets for therapeutic intervention. In spite of the recent advancements in membrane protein crystallography, limited information is available on the molecular signatures of activation of GPCRs. Corticotropin-releasing factor 1 receptor (CRF1R), a class B GPCR, is associated with various disease conditions including stress, anxiety, and irritable bowel syndrome.

PSII–LHCII Supercomplex Organizations in Photosynthetic Membrane by Coarse-Grained Simulation

Cheng-Kuang Lee, Chun-Wei Pao, Berend Smit [Institut des Sciences et Ingénierie Chimiques (ISIC)]

J. Phys. Chem. B., **119**, 3999–4008, 2015.

Green plant photosystem II (PSII) and light-harvesting complex II (LHCII) in the stacked grana regions of thylakoid membranes can self-organize into various PSII–LHCII supercomplexes with crystalline or fluid-like supramolecular structures to adjust themselves with external stimuli such as high/low light and temperatures, rendering tunable solar light absorption spectrum and photosynthesis efficiencies. However, the mechanisms controlling the PSII–LHCII supercomplex organizations remain elusive. In this work, we constructed a coarse-grained (CG) model of the thylakoid membrane including lipid molecules and a PSII–LHCII supercomplex considering association/dissociation of moderately bound-LHCII.

Ionic Clusters vs Shear Viscosity in Aqueous Amino Acid Ionic Liquids

Vitaly V. Chaban, Eudes Eterno Fileti [Universidade Federal de São Paulo]

J. Phys. Chem. B., **119**, 3824–3828, 2015.

Aqueous solutions of amino acid ionic liquids (AAILs) are of high importance for applications in protein synthesis and solubilization, enzymatic reactions, templates for synthetic study, etc. This work employs molecular dynamics simulations using our own force field to investigate shear viscosity and cluster compositions of three 1-ethyl-3-methylimidazolium (emim) amino acid salts: [emim][ala], [emim][met], and [emim][trp] solutions (2, 5, 10, 20, and 30 mol %) in water at 310 K.

Guided Ion Beam and Computational Studies of the Decomposition of a Model Thiourea Protein Cross-Linker

Ran Wang, Bo Yang, R. R. Wu, M. T. Rodgers, M. Schäfer, P. B. Armentrout [University of Utah]

J. Phys. Chem. B., **119**, 3727–3742, 2015.

The dissociation of protonated methyl-d3 thiourea-4-butyric acid methyl amide (1), a model of thiourea-based protein cross-linking compounds, is examined both experimentally and computationally. Using a guided ion beam tandem mass spectrometer (GIBMS), the threshold collision-induced dissociation (TCID) of $[1 + H]^+$ with Xe is examined as a function of collision energy. Analysis of the kinetic energy-dependent CID cross sections provides the 0 K barriers for four primary and four secondary dissociation pathways, after accounting for competition between channels, sequential dissociations, unimolecular decay rates, internal energy.

Protein Dynamics (Cont'd)

Dihedral Angle Entropy Measures for Intrinsically Disordered Proteins

Robert I. Cukier [Michigan State University]

J. Phys. Chem. B., **119**, 3621–3634, 2015.

Protein stability is based on a delicate balance between energetic and entropic factors. Intrinsically disordered proteins (IDPs) interacting with a folded partner protein in the act of binding can order the IDP to form the correct functional interface by decrease in the overall free energy. In this work, we evaluate the part of the entropic cost of ordering an IDP arising from their dihedral states. The IDP studied is a leucine zipper dimer that we simulate with molecular dynamics and find that it does show disorder in six phi and psi dihedral angles of the N terminal sequence of one monomer. Essential to ascertain is the degree of disorder in the IDP, and we do so by considering the entire, discretized probability distribution function of N dihedrals with M conformers per dihedral.

The Hole in the Barrel: Water Exchange at the GFP Chromophore

Ai Shinobu , Noam Agmon [The Hebrew University of Jerusalem]

J. Phys. Chem. B., **119**, 3464–3478 , 2015.

Internal water molecules in proteins are conceivably part of the protein structure, not exchanging easily with the bulk. We present a detailed molecular dynamics study of the water molecule bound to the green fluorescent protein (GFP) chromophore that conducts its proton following photoexcitation. It readily exchanges above 310 K through a hole that forms between strands 7 and 10, due to fluctuations in the 6–7 loop. As the hole widens, rapid succession of water exchange events occur. The exiting water molecule passes three layers of atoms, constituting the binding, internal, and surface sites. Along this pathway, hydrogen bonding protein residues are replaced with water molecules.

Phosphorylation as Conformational Switch from the Native to Amyloid State: Trp-Cage as a Protein Aggregation Model

József Kardos, Bence Kiss, András Micsonai, Petra Rovó, Dóra K. Menyhárd, János Kovács, Györgyi Váradi, Gábor K. Tóth, András Perczel[Eötvös Loránd University]

J. Phys. Chem. B., **119**, 2946–2955, 2015.

The 20 residue long Trp-cage miniprotein is an excellent model for both computational and experimental studies of protein folding and stability. Recently, great attention emerged to study disease-related protein misfolding, aggregation, and amyloid formation, with the aim of revealing their structural and thermodynamic background. Trp-cage is sensitive to both environmental and structure-modifying effects. It aggregates with ease upon structure destabilization, and thus it is suitable for modeling aggregation and amyloid formation. Here, we characterize the amyloid formation of several sequence modified and side-chain phosphorylated Trp-cage variants.

Protein Dynamics (Cont'd)

Local elastic constants of LacI and implications for allostery

Andre A.S.T. Ribeiro, Vanessa Ortiz[Columbia University]

J. Mol.Graph. and Mod., **57**, 106-113,2015.

Allostery connects subtle changes in a protein's potential energy surface, induced by perturbations like ligand-binding, to significant changes in its function. Understanding this phenomenon and predicting its occurrence are major goals of current research in biophysics and molecular biology. In this paper we introduce a novel approach for studying complex structural transformations such as those typical for allostery. We show that the calculation and analysis of atomic elastic constants of a known allosterically regulated protein, lac repressor, highlights regions that are particularly prone to suffer structural deformation and are experimentally linked to allosteric function.

Decoding the Mobility and Time Scales of Protein Loops

Yina Gu, Da-Wei Li, Rafael Brüschweiler [The Ohio State University]

J. Chem. Theor. and Comp, **11**, 1308–1314, 2015.

The flexible nature of protein loops and the time scales of their dynamics are critical for many biologically important events at the molecular level, such as protein interaction and recognition processes. In order to obtain a predictive understanding of the dynamic properties of loops, 500 ns molecular dynamics (MD) computer simulations of 38 different proteins were performed and validated using NMR chemical shifts. A total of 169 loops were analyzed and classified into three types, namely fast loops with correlation times <10 ns, slow loops with correlation times between 10 and 500 ns, and loops that are static over the course of the whole trajectory.

Influence of Antifreeze Proteins on the Ice/Water Interface

Guido Todde, Sven Hovmöller, Aatto Laaksonen [Stockholm University]

J. Phys. Chem. B., **119**, 3407–3413, 2015.

Antifreeze proteins (AFP) are responsible for the survival of several species, ranging from bacteria to fish, that encounter subzero temperatures in their living environment. AFPs have been divided into two main families, moderately and hyperactive, depending on their thermal hysteresis activity. We have studied one protein from both families, the AFP from the snow flea (sfAFP) and from the winter flounder (wfAFP), which belong to the hyperactive and moderately active family, respectively. On the basis of molecular dynamics simulations, we have estimated the thickness of the water/ice interface for systems both with and without the AFPs attached onto the ice surface.

Protein Dynamics (Cont'd)

Structural dynamics of native and V260E mutant C-terminal domain of HIV-1 integrase

Balasubramanian Sangeetha, Rajagopalan Muthukumaran, Ramaswamy Amutha[Pondicherry University]

J.Comp.Aided. Mol.des. **29**, 371-385, 2015.

The C-terminal domain (CTD) of HIV-1 integrase is a five stranded β -barrel resembling an SH3 fold. Mutational studies on isolated CTD and full-length IN have reported V260E mutant as either homo-dimerization defective or affecting the stability and folding of CTD. In this study, molecular dynamics simulation techniques were used to unveil the effect of V260E mutation on isolated CTD monomer and dimer. Both monomeric and dimeric forms of wild type and V260E mutant are highly stable during the simulated period. However, the stabilizing π -stacking interaction between Trp243 and Trp243' at the dimer interface is highly disturbed in CTD-V260E (>6 Å apart).

Ligand Binding/Docking

In silico identification of novel ligands for G-quadruplex in the c-MYC promoter

Hyun-Jin Kang, Hyun-Ju Park [Sungkyunkwan University]

J.Comp.Aided. Mol.des. **29**, 339-348, 2015.

G-quadruplex DNA formed in NHEIII1 region of oncogene promoter inhibits transcription of the genes. In this study, virtual screening combining pharmacophore-based search and structure-based docking screening was conducted to discover ligands binding to G-quadruplex in promoter region of c-MYC. Several hit ligands showed the selective PCR-arresting effects for oligonucleotide containing c-MYC G-quadruplex forming sequence. Among them, three hits selectively inhibited cell proliferation and decreased c-MYC mRNA level in Ramos cells, where NHEIII1 is included in translocated c-MYC gene for overexpression.

Human PD-1 binds differently to its human ligands: A comprehensive modeling study

Clement Viricel, Marawan Ahmed, Khaled Barakat[University of Alberta]

J. Mol.Graph. and Mod., **57**, 131-142,2015.

Programmed death-1 (PD-1) is a potent inhibitory receptor of T cells which binds to two different ligands, namely PD-L1 and PD-L2, and upon binding, it inhibits T cell activation, differentiation, and proliferation, leading to a state of immune tolerance. Blocking these interactions recently emerged as a 'game changer' approach in immunotherapy. Here we describe for the first time two accurate models for human PD-1 bound to its two human ligands. Our methodology involved combining molecular dynamics (MD) simulations with protein-protein docking and binding energy analysis to predict the most probable binding conformations for PD1 to its ligands.

Enzyme Catalysis

Molecular modeling and identification of novel glucokinase activators through stepwise virtual screening

Pabitra Mohan Behera, Deepak Kumar Behera, Suresh Satpati, Geetanjali Agnihotri, Sanghamitra Nayak, Payodhar Padhi, Anshuman Dixit [Institute of Life Sciences, Nalco Square, Bhubaneswar]

J. Mol. Graph. and Mod., **57**, 122-130, 2015.

The glucose phosphorylating enzyme glucokinase (GK) is a 50 kD monomeric protein having 465 amino acids. It maintains glucose homeostasis inside cells, acts as a glucose sensor in pancreatic β -cells and as a rate controlling enzyme for hepatic glucose clearance and glycogen synthesis. It has two binding sites, one for binding D-glucose and the other for a putative allosteric activator named glucokinase activator (GKA). The GKAs interact with the same region of the GK enzyme that is commonly affected by naturally occurring mutations in humans. In this milieu a molecular modeling study has been carried out on three natural variants of GK that lie in the GKA binding site and are known to cause maturity onset diabetes of young (MODY).

MetREx: A protein design approach for the exploration of sequence-reactivity relationships in metalloenzymes

Martin T. Stiebritz [Laboratorium für Physikalische Chemie, ETH Zürich]

J. Comp. Chem., **36**, 553–563, 2015.

Metalloenzymes represent a particular challenge for any rational (re)design approach because the modeling of reaction events at their metallic cofactors requires time-consuming quantum mechanical calculations, which cannot easily be reconciled with the fast, knowledge-based approaches commonly applied in protein design studies. Here, an approach for the exploration of sequence-reactivity relationships in metalloenzymes is presented (MetREx) that consists of force field-based screening of mutants that lie energetically between a wild-type sequence and the global minimum energy conformation and which should, therefore, be compatible with a given protein fold.

Comparative Modeling and Benchmarking Data Sets for Human Histone Deacetylases and Sirtuin Families

Jie Xia, Ermias Lemma Tilahun, Eyob Hailu Kebede, Terry-Elinor Reid, Liangren Zhang, Xiang Simon Wang [Howard University]

J. Chem. Infor. and Mod. **55**, 374–388, 2015.

Histone deacetylases (HDACs) are an important class of drug targets for the treatment of cancers, neurodegenerative diseases, and other types of diseases. Virtual screening (VS) has become fairly effective approaches for drug discovery of novel and highly selective histone deacetylase inhibitors (HDACIs). To facilitate the process, we constructed maximal unbiased benchmarking data sets for HDACs (MUBD-HDACs) using our recently published methods that were originally developed for building unbiased benchmarking sets for ligand-based virtual screening (LBVS). The MUBD-HDACs cover all four classes including Class III (Sirtuins family) and 14 HDAC isoforms, composed of 631 inhibitors and 24 609 unbiased decoys.

Enzyme Catalysis (Cont'd)

On the Challenge of Exploring the Evolutionary Trajectory from Phosphotriesterase to Arylesterase Using Computer Simulations

Ram Prasad Bora, Matthew J. L. Mills, Maria P. Frushicheva, Arieh Warshel [University of Southern California]

J. Phys. Chem. B., **119**, 3434–3445, 2015.

The ability to design effective enzymes presents a fundamental challenge in biotechnology and also in biochemistry. Unfortunately, most of the progress on this field has been accomplished by bringing the reactants to a reasonable orientation relative to each other, rather than by rational optimization of the polar preorganization of the environment, which is the most important catalytic factor. True computer based enzyme design would require the ability to evaluate the catalytic power of designed active sites. This work considers the evolution from a phosphotriesterase (with the paraoxon substrate) to arylesterase (with the 2-naphthylhexanoate (2NH) substrate) catalysis.

Enzyme Homologues Have Distinct Reaction Paths through Their Transition States

Ioanna Zoi, Matthew W. Motley, Dimitri Antoniou, Vern L. Schramm, Steven D. Schwartz [University of Arizona]

J. Phys. Chem. B., **119**, 3662–3668, 2015.

Recent studies of the bacterial enzymes EcMTAN and VcMTAN showed that they have different binding affinities for the same transition state analogue. This was surprising given the similarity of their active sites. We performed transition path sampling simulations of both enzymes to reveal the atomic details of the catalytic chemical step, which may be the key for explaining the inhibitor affinity differences. Even though all experimental data would suggest the two enzymes are almost identical, subtle dynamic differences manifest in differences of reaction coordinate, transition state structure, and eventually significant differences in inhibitor binding.

Computational Analysis of Ammonia Transfer Along Two Intramolecular Tunnels in *Staphylococcus aureus* Glutamine-Dependent Amidotransferase (GatCAB)

Sajeewa Walimuni Dewage, G. Andrés Cisneros [Wayne State University]

J. Phys. Chem. B., **119**, 3669–3677, 2015.

Most bacteria and all archaea misacylate the tRNAs corresponding to Asn and Gln with Asp and Glu (Asp-tRNA^{Asn} and Glu-tRNA^{Gln}). The GatCAB enzyme of most bacteria converts misacylated Glu-tRNA^{Gln} to Gln-tRNA^{Gln} in order to enable the incorporation of glutamine during protein synthesis. The conversion process involves the intramolecular transfer of ammonia between two spatially separated active sites. This study presents a computational analysis of the two putative intramolecular tunnels that have been suggested to describe the ammonia transfer between the two active sites.

Enzyme Catalysis (Cont'd)

Structure based virtual screening to identify selective phosphodiesterase 4B inhibitors

Rahul P. Gangwal, Mangesh V. Damre, Nihar R. Das, Gaurao V. Dhoke, Anuseema Bhadauriya, Rohith A. Varikoti, Shyam S. Sharma, Abhay T. Sangamwar[National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Graph. and Mod., **57**, 89-98,2015.

Phosphodiesterase 4 (PDE4), is a hydrolytic enzyme, is proposed as a promising target in asthma and chronic obstructive pulmonary disease. PDE4B selective inhibitors are desirable to reduce the dose limiting adverse effect associated with non-selective PDE4B inhibitors. To achieve this goal, ligand based pharmacophore modeling and molecular docking approach is employed. Pharmacophore hypotheses for PDE4B and PDE4D are generated using HypoGen algorithm. The best PDE4B pharmacophore hypothesis (Hypo1_PDE4B) consist of one hydrogen-bond acceptor and two ring aromatic features, whereas PDE4D pharmacophore hypothesis (Hypo1_PDE4D) consist of one hydrogen-bond acceptor, one hydrophobic aliphatic, and two ring aromatic features.

Protein-Protein Interactions

Molecular recognition of avirulence protein (avrxa5) by eukaryotic transcription factor xa5 of rice (*Oryza sativa* L.): Insights from molecular dynamics simulations

Budheswar Dehury, Jitendra Maharana, Bikash Ranjan Sahoo, Jagajjit Sahu, Priyabrata Sen, Mahendra Kumar Modi, Madhumita Barooah[Assam Agricultural University]

J. Mol.Graph. and Mod., **57**, 49-61,2015.

The avirulence gene *avrxa5* of bacterial blight pathogen *Xanthomonas oryzae* pv. *oryzae* (Xoo) recognized by the resistant rice lines having corresponding resistance (*xa5*) gene in a gene-for-gene manner. We used a combinatorial approach involving protein-protein docking, molecular dynamics (MD) simulations and binding free energy calculations to gain novel insights into the gene-for-gene mechanism that governs the direct interaction of R-Avr protein. From the best three binding poses predicted by molecular docking, MD simulations were performed to explore the dynamic binding mechanism of *xa5* and *avrxa5*.

Protein-Protein Interactions Affect Alpha Helix Stability in Crowded Environments

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

J. Phys. Chem. B., **119**, 2956–2967, 2015.

The dense, heterogeneous cellular environment is known to affect protein stability through interactions with other biomacromolecules. The effect of excluded volume due to these biomolecules, also known as crowding agents, on a protein of interest, or test protein, has long been known to increase the stability of a test protein. Recently, it has been recognized that attractive protein-crowder interactions play an important role. These interactions affect protein stability and can destabilize the test protein. However, most computational work investigating the role of attractive interactions has used spherical crowding agents and has neglected the specific roles of crowding agent hydrophobicity and hydrogen bonding.

Membrane Proteins and Lipid Peptide Interactions

Peptide-induced formation of a tethered lipid bilayer membrane on mesoporous silica

Maria Wallin, Jae-Hyeok Choi, Seong Oh Kim, Nam-Joon Cho, Martin Andersson [Chalmers University of Technology]

Eur.Biophy., **44**, 27-36, 2015.

Tethered bilayer lipid membranes (tBLMs) on solid supports have substantial advantages as models of artificial cell membranes for such biomedical applications as drug delivery and biosensing. Compared with untethered lipid membranes, tBLMs have more space between substrate and the bilayer and greater stability. The purpose of this work was to use these properties to fabricate and characterize a zwitterionic 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine lipid tBLM containing 2 mol % 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-maleimide(poly(ethylene glycol))-2000 (DSPE-PEG2000-NHS) lipid tethers on a 3-aminopropyltrimethoxysilane-modified mesoporous silica substrate.

Free energy simulations of amylin I26P mutation in a lipid bilayer

Seifollah Jalili, Afsaneh Maleki [Islamic Azad University], Mojdeh Akhavan, Bijan Najafi, Jeremy Schofield

Eur.Biophy., **44**, 37-47, 2015.

The amylin peptide in a dioleoylphosphatidylcholine (DOPC) bilayer is studied using united atom molecular dynamics (MD) simulations. Dynamics and transport properties of the peptide and the phospholipid bilayer are investigated. The lateral diffusion of DOPC is in the order of 10^{-8} cm² s⁻¹, which is in agreement with the experimental results. The order parameter and density profile for phospholipid molecules in the bilayer are calculated. The secondary structure of amylin peptide shows that the amino acids in two terminals are structureless and two α -helical segments in the peptide are connected through an unstructured link.

Spatial Analysis and Quantification of the Thermodynamic Driving Forces in Protein-Ligand Binding: Binding Site Variability

E. Prabhu Raman [University of Maryland School of Pharmacy], Alexander D. MacKerell, Jr.

J. Am. Chem. Soc., **137**, 2608–2621, 2015.

The thermodynamic driving forces behind small molecule-protein binding are still not well-understood, including the variability of those forces associated with different types of ligands in different binding pockets. To better understand these phenomena we calculate spatially resolved thermodynamic contributions of the different molecular degrees of freedom for the binding of propane and methanol to multiple pockets on the proteins Factor Xa and p38 MAP kinase. Binding thermodynamics are computed using a statistical thermodynamics based end-point method applied on a canonical ensemble comprising the protein-ligand complexes and the corresponding free states in an explicit solvent environment.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Analyzing Multitarget Activity Landscapes Using Protein–Ligand Interaction Fingerprints: Interaction Cliffs

Oscar Méndez-Lucio, Albert J. Kooistra, Chris de Graaf, Andreas Bender, José L. Medina-Franco [Universidad Nacional Autónoma de México]

J.Chem. Infor. and Mod. **55**, 251–262, 2015.

Activity landscape modeling is mostly a descriptive technique that allows rationalizing continuous and discontinuous SARs. Nevertheless, the interpretation of some landscape features, especially of activity cliffs, is not straightforward. As the nature of activity cliffs depends on the ligand and the target, information regarding both should be included in the analysis. A specific way to include this information is using protein–ligand interaction fingerprints (IFPs). In this paper we report the activity landscape modeling of 507 ligand–kinase complexes (from the KLIFS database) including IFP, which facilitates the analysis and interpretation of activity cliffs.

Performance of Protein–Ligand Docking with Simulated Chemical Shift Perturbations

Tim ten Brink, Clémentine Aguirre, Thomas E. Exner, Isabelle Krimm [Université Lyon 1]

J.Chem. Infor. and Mod. **55**, 275–283, 2015.

Protein chemical shift perturbations (CSPs) that result from the binding of a ligand to the protein contain structural information about the complex. Therefore, the CSP data, typically obtained during library screening from two-dimensional (2D) nuclear magnetic resonance (NMR) spectra, are often available before attempts to solve the experimental structure of the complex are started, and can be used to solve the complex structure with CSP-based docking. Here, we compare the performance of the post-docking filter and the guided-docking approaches using either amide or α -proton CSPs with 10 protein–ligand complexes.

Potential Application of Alchemical Free Energy Simulations to Discriminate GPCR Ligand Efficacy

Hui Sun Lee, Chaok Seok, Wonpil Im [The University of Kansas]

J. Chem. Theor. and Comp. **11**, 1255–1266, 2015.

G protein-coupled receptors (GPCRs) play fundamental roles in physiological processes by modulating diverse signaling pathways and thus have been one of the most important drug targets. Based on the fact that GPCR-mediated signaling is modulated in a ligand-specific manner such as agonist, inverse agonist, and neutral antagonist (termed ligand efficacy), quantitative characterization of the ligand efficacy is essential for rational design of selective modulators for GPCR targets. Here, we have performed free energy perturbation molecular dynamics simulations to calculate absolute binding free energy of an inverse agonist, a neutral antagonist, and an agonist to β 2-adrenergic receptor (β 2-AR) active and inactive states, respectively, in explicit lipid bilayers.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Measurement of the Membrane Dipole Electric Field in DMPC Vesicles Using Vibrational Shifts of p-Cyanophenylalanine and Molecular Dynamics Simulations

Rebika Shrestha, Alfredo E. Cardenas, Ron Elber, Lauren J. Webb[The University of Texas at Austin]

J. Phys. Chem. B., **119**, 2869–2876, 2015.

The magnitude of the membrane dipole field was measured using vibrational Stark effect (VSE) shifts of nitrile oscillators placed on the unnatural amino acid p-cyanophenylalanine (p-CN-Phe) added to a peptide sequence at four unique positions. These peptides, which were based on a repeating alanine-leucine motif, intercalated into small unilamellar DMPC vesicles which formed an α -helix as confirmed by circular dichroic (CD) spectroscopy. Molecular dynamics simulations of the membrane-intercalated helix containing two of the nitrile probes, one near the headgroup region of the lipid (α LAX(25)) and one buried in the interior of the bilayer (α LAX(16)).

Interactions of Amino Acid Side-Chain Analogs within Membrane Environments

Vahid Mirjalili, Michael Feig[Michigan State University]

J. Phys. Chem. B., **119**, 2877–2885, 2015.

The interactions among four amino acid analog pairs (Asn, Ser, Phe, and Val) within the membrane environment were investigated using umbrella sampling molecular dynamics simulations. The results confirm generally expected qualitative trends of preferential association of polar compounds inside the membrane vs preferential interaction of hydrophobic compounds outside the membrane. Furthermore, correlations between amino acid interactions, membrane insertion, and membrane deformations are discussed and a detailed analysis of pair interaction energies is presented.

Molecular Organization of Nalidixate Conjugated Calixarenes in Bacterial Model Membranes Probed by Molecular Dynamics Simulation and Langmuir Monolayer Studies

Beata Korchowiec, Jacek Korchowiec, Marcelina Gorczyca, Jean-Bernard Regnouf de Vains, Ewa Rogalska [CNRS/Université de Lorraine]

J. Phys. Chem. B., **119**, 2990–3000, 2015.

Two p-tert-butylcalix[4]arene derivatives bearing one or two nalidixic acid groups connected to the lower rim of p-tert-butylcalix[4]arene through the propylenic spacer were studied upon interaction with model bacterial membranes. Indeed, these derivatives were developed recently as new macrocyclic antibiotic carriers for antibacterial therapy. To obtain molecular level information about the interaction between the calixarene conjugates and a membrane lipid, atomistic molecular dynamics simulation, as well as surface pressure, surface potential, polarization modulation infrared reflection-absorption spectroscopy, and Brewster angle microscopy studies of 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE)-calixarene derivative films were performed.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Distinct Helix Propensities and Membrane Interactions of Human and Rat IAPP1–19 Monomers in Anionic Lipid Bilayers

Cong Guo, Sébastien Côté, Normand Mousseau, Guanghong Wei [Fudan University]

J. Phys. Chem. B., **119**, 3366–3376 , 2015.

Islet amyloid polypeptide, IAPP or amylin, is a 37-residue peptide hormone coexpressed with insulin by pancreatic β -cells. The aggregation of human IAPP (hIAPP) into amyloid deposits is associated with type II diabetes. Substantial evidence suggests that the interaction of anionic membranes with hIAPP may facilitate peptide aggregation and the N-terminal 1–19 fragment (IAPP1–19) plays an important role in peptide–membrane interaction. As a first step to understand how structural differences between human and rat IAPP peptides in membranes may influence the later oligomerization process, we have investigated the structures and orientations of hIAPP1–19 and the less toxic rIAPP1–19 (i.e., the H18R mutant of hIAPP1–19) monomers in anionic POPG bilayers by performing replica exchange molecular dynamics (REMD) simulations.

Protein Folding

Dependence of Internal Friction on Folding Mechanism

Wenwei Zheng, David De Sancho, Travis Hoppe, Robert B. Best [National Institutes of Health, Bethesda]

J. Am. Chem. Soc., **137**, 3283–3290, 2015.

An outstanding challenge in protein folding is understanding the origin of “internal friction” in folding dynamics, experimentally identified from the dependence of folding rates on solvent viscosity. A possible origin suggested by simulation is the crossing of local torsion barriers. However, it was unclear why internal friction varied from protein to protein or for different folding barriers of the same protein. Using all-atom simulations with variable solvent viscosity, in conjunction with transition-path sampling to obtain reaction rates and analysis via Markov state models, we are able to determine the internal friction in the folding of several peptides and miniproteins.

Protein-Nucleic acid Interactions

Role of indirect readout mechanism in TATA box binding protein–DNA interaction

Manas Mondal, Devapriya Choudhury, Jaydeb Chakrabarti, Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics]

J.Comp.Aided. Mol.des. **29**, 283-295, 2015.

Gene expression generally initiates from recognition of TATA-box binding protein (TBP) to the minor groove of DNA of TATA box sequence where the DNA structure is significantly different from B-DNA. We have carried out molecular dynamics simulation studies of TBP–DNA system to understand how the DNA structure alters for efficient binding. We observed rigid nature of the protein while the DNA of TATA box sequence has an inherent flexibility in terms of bending and minor groove widening.

Protein-Nucleic Acid Interactions (Cont'd)

Can We Execute Stable Microsecond-Scale Atomistic Simulations of Protein–RNA Complexes?

M. Krepl, M. Havrila, P. Stadlbauer, P. Banas, M. Otyepka, J. Pasulka, R. Stefl, J. Sponer [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp., **11**, 1220–1243, 2015.

We report over 30 μ s of unrestrained molecular dynamics simulations of six protein–RNA complexes in explicit solvent. We utilize the AMBER ff99bsc0 χ OL3 RNA force field combined with the ff99SB protein force field and its more recent ff12SB version with reparametrized side-chain dihedrals. The simulations show variable behavior, ranging from systems that are essentially stable to systems with progressive deviations from the experimental structure, which we could not stabilize anywhere close to the starting experimental structure. For some systems, microsecond-scale simulations are necessary to achieve stabilization after initial sizable structural perturbations.

DNA Bases Assembled on the Au(110)/Electrolyte Interface: A Combined Experimental and Theoretical Study

Princia Salvatore, Renat R. Nazmutdinov, Jens Ulstrup, Jingdong Zhang [Technical University of Denmark]

J. Phys. Chem. B., **119**, 3123–3134, 2015.

Among the low-index single-crystal GOLD surfaces, the Au(110) surface is the most active toward molecular adsorption and the one with fewest electrochemical adsorption data reported. Cyclic voltammetry (CV), electrochemically controlled scanning tunneling microscopy (EC–STM), and density functional theory (DFT) calculations have been employed in the present study to address the adsorption of the four nucleobases adenine (A), cytosine (C), guanine (G), and thymine (T), on the Au(110)-electrode surface. Au(110) undergoes reconstruction to the (1 $\times$ 3) surface in electrochemical environment, accompanied by a pair of strong voltammetry peaks in the double-layer region in acid solutions.

Native Conformational Dynamics of the Spliceosomal U1A Protein

Irisbel Guzman, Zhaleh Ghaemi, Anne Baranger, Zaida Luthey-Schulten, Martin Gruebele [University of Illinois]

J. Phys. Chem. B., **119**, 3651–3661, 2015.

The complex of spliceosomal U1A protein and its cognate SL2 RNA is a prototype system for protein–RNA binding studies. A major question is whether U1A protein alone is capable of undergoing conformational dynamics similar to structural rearrangements upon RNA binding. Using a fast temperature jump and tryptophan fluorescence detection, we uncover a $\sim$ 20 μ s conformational transition for the Lys22Gln/Phe56Trp-only mutant of U1A, yet a Phe56Trp-only control mutant does not show the transition. To explain this observation, we performed extensive molecular dynamics (MD) simulations.

Caffeine's Antioxidant Potency Optically Sensed with Double-Stranded DNA-Encased Single-Walled Carbon Nanotubes

Edward H. Zhao, Busra Ergul, Wei Zhao [University of Arkansas at Little Rock]

J. Phys. Chem. B., **119**, 4068–4075, 2015.

There is great interest in developing a sensitive method being able to quantitatively measure and compare antioxidant potencies of samples of interest against multiple reactive oxygen species (ROS) whose imbalance could cause oxidative stress. Here, a sensitive nanoprobe, double-stranded DNA encased single-walled carbon nanotubes (SWNTs) has been developed to determine antioxidant potencies of selected samples (caffeine, regular coffee, and decaffeinated coffee) against ROS, hydrogen peroxide, and hydroxyl radicals. Antioxidant vitamin C and uric acid are used as standards.

Nucleic Acids

Naturally occurring polyphenol, morin hydrate, inhibits enzymatic activity of N-methylpurine DNA glycosylase, a DNA repair enzyme with various roles in human disease

Monica Dixon, Jordan Woodrick, Suhani Gupta, Soumendra Krishna Karmahapatra, Stephen Devito, Sona Vasudevan, Sivanesan Dakshanamurthy, Sanjay Adhikari, Venkata M. Yenugonda, Rabindra Roy [Georgetown University]

Bioorg. and Med.Chem., **23**, 1102-1111, 2015.

Interest in the mechanisms of DNA repair pathways, including the base excision repair (BER) pathway specifically, has heightened since these pathways have been shown to modulate important aspects of human disease. Modulation of the expression or activity of a particular BER enzyme, N-methylpurine DNA glycosylase (MPG), has been demonstrated to play a role in carcinogenesis and resistance to chemotherapy as well as neurodegenerative diseases, which has intensified the focus on studying MPG-related mechanisms of repair. A specific small molecule inhibitor for MPG activity would be a valuable biochemical tool for understanding these repair mechanisms.

Insights into the preferential order of strand exchange in the Cre/loxP recombinase system: impact of the DNA spacer flanking sequence and flexibility

Josephine Abi-Ghanem, Sergey A. Samsonov, M. Teresa Pisabarro [Biotec TU Dresden]

J.Comp.Aided. Mol.des. **29**, 13-21, 2015.

The Cre/loxP system is widely used as a genetic tool to manipulate DNA. Cre recombinase catalyzes site-specific recombination between 34 bp loxP sites. Each loxP site is recognized by two Cre molecules assuming a cleaving (CreC) and non-cleaving (CreNC) activity. We apply computational structure-based methods and perform a thorough detailed analysis of available structural and biochemical information on the Cre/loxP system in order to investigate such asymmetry in the recombination, and we propose a rationale to explain the determinants favoring the strand exchange order.

Theoretical Study of Structural Changes in DNA under High External Hydrostatic Pressure

P. Sudheer Kumar, Arnab Mukherjee, Anirban Hazra [Indian Institute of Science Education and Research, Pune]

J. Phys. Chem. B., **119**, 3348–3355, 2015.

The study of DNA under high hydrostatic pressure provides fundamental insights into the nature of interactions responsible for its structure and its remarkable stability in extreme conditions. We have investigated the structural changes in DNA under 2000 bar external pressure using electronic structure calculations and molecular dynamics simulations. Both these methods predict very small distortions in the structure; notably, the change in hydrogen bond lengths is an order of magnitude smaller than previously reported experimental values using NMR.

Two-Quartet G-Quadruplexes Formed by DNA Sequences Containing Four Contiguous GG Runs

Mingyan Qin, Zhuxi Chen, Qichao Luo, Yi Wen, Naixia Zhang, Hualiang Jiang, Huaiyu Yang [Chinese Academy of Sciences]

J. Phys. Chem. B., **119**, 3706–3713, 2015.

The DNA sequence containing four contiguous GG runs (G2NxG2NyG2NzG2, G2 sequence) has the potential to form a two-quartet G-quadruplex. However, the prevalence, structure, and function of G2 sequences have not been well-studied. Here, bioinformatics analysis reveals the abundance of G2 sequences in the human genome and their enrichment in promoter regions. The density of G2 sequences in the genome and promoters is much higher than that of the G3 sequence (G3NxG3NyG3NzG3). Experiments show that the conformations and thermal stabilities of the two-quartet G-quadruplexes of G2 sequences are highly sensitive to the length and composition of the loops.

Surfaces, Catalysts, and Materials Subjects

Adsorption of Proteins at the Solution/Air Interface Influenced by Added Nonionic Surfactants at Very Low Concentrations for Both Components. 3. Dilational Surface Rheology

V. B. Fainerman, E. V. Aksenenko, S. V. Lylyk, M. Lotfi, and R. Miller [Sharif University of Technology]

J. Phys. Chem. B., **119**, 3768–3775, 2015.

The influence of the addition of the nonionic surfactants C12DMPO, C14DMPO, C10OH, and C10EO5 at concentrations between 10⁻⁵ and 10⁻¹ mmol/L to solutions of β -casein (BCS) and β -lactoglobulin (BLG) at a fixed concentration of 10⁻⁵ mmol/L on the dilational surface rheology is studied. A maximum in the viscoelasticity modulus $|E|$ occurs at very low surfactant concentrations (10⁻⁴ to 10⁻³ mmol/L) for mixtures of BCS with C12DMPO and C14DMPO and for mixtures of BLG with C10EO5, while for mixture of BCS with C10EO5 the value of $|E|$ only slightly increased.

2. METHODOLOGY

Quantitative Structure-Activity Relations

QSAR model as a random event: A case of rat toxicity

Alla P. Toropova, Andrey A. Toropov [IRCCS—Istituto di Ricerche Farmacologiche Mario Negri], Emilio Benfenati, Danuta Leszczynska, Jerzy Leszczynski

Bioorg. and Med.Chem., **23**, 1223-1230 ,2015.

Quantitative structure—property/activity relationships (QSPRs/QSARs) can be used to predict physicochemical and/or biochemical behavior of substances which were not studied experimentally. Typically predicted values for chemicals in the training set are accurate since they were used to build the model. QSPR/QSAR models must be validated before they are used in practice. Unfortunately, the majority of the suggested approaches of the validation of QSPR/QSAR models are based on consideration of geometrical features of clusters of data points in the plot of experimental versus calculated values of an endpoint.

A probabilistic method to report predictions from a human liver microsomes stability QSAR model: a practical tool for drug discovery

Ignacio Aliagas [Genentech Inc], Alberto Gobbi, Timothy Heffron, Man-Ling Lee, Daniel F. Ortwine, Mark Zak, S. Cyrus Khojasteh

J.Comp.Aided. Mol.des. **29**, 327-338, 2015.

Using data from the in vitro liver microsomes metabolic stability assay, we have developed QSARmodels to predict in vitro human clearance. Models were trained using in house high-throughput assay data reported as the predicted human hepatic clearance by liver microsomes or pCLh. Machine learning regression methods were used to generate the models. Model output for a given molecule was reported as its probability of being metabolically stable, thus allowing for synthesis prioritization based on this prediction. Use of probability, instead of the regression value or categories, has been found to be an efficient way for both reporting and assessing predictions. Model performance is evaluated using prospective validation.

Quantitative Structure-Activity Relations (Cont'd)

Deep Neural Nets as a Method for Quantitative Structure–Activity Relationships

Junshui Ma [Merck Research Laboratories], Robert P. Sheridan, Andy Liaw, George E. Dahl, Vladimir Svetnik

J.Chem. Infor. and Mod. **55**, 263–274, 2015.

Neural networks were widely used for quantitative structure–activity relationships (QSAR) in the 1990s. Because of various practical issues (e.g., slow on large problems, difficult to train, prone to overfitting, etc.), they were superseded by more robust methods like support vector machine (SVM) and random forest (RF), which arose in the early 2000s. Here we show that DNNs can routinely make better prospective predictions than RF on a set of large diverse QSAR data sets that are taken from Merck’s drug discovery effort.

Potentials and Parameters

Bottom-Up Coarse-Graining of Peptide Ensembles and Helix–Coil Transitions

Joseph F. Rudzinski William G. Noid [The Pennsylvania State University]

J. Chem. Theor. and Comp. **11**, 1278–1291, 2015.

This work investigates the capability of bottom-up methods for parametrizing minimal coarse-grained (CG) models of disordered and helical peptides. We consider four high-resolution peptide ensembles that demonstrate varying degrees of complexity. For each high-resolution ensemble, we parametrize a CG model via the multiscale coarse-graining (MS-CG) method, which employs a generalized Yvon–Born–Green (g-YBG) relation to determine potentials directly (i.e., without iteration) from the high-resolution ensemble. The MS-CG method accurately describes high-resolution models that fluctuate about a single conformation.

Coarse-Grain Simulations of Skin Ceramide NS with Newly Derived Parameters Clarify Structure of Melted Phase

Žofie Sovová, Karel Berka, Michal Otyepka[Palacký University], Petr Jurečka

J. Phys. Chem. B. **119**, 3988–3998, 2015.

Ceramides are lipids that are involved in numerous biologically important structures (e.g., the stratum corneum and ceramide-rich platforms) and processes (e.g., signal transduction and membrane fusion), but their behavior is not fully understood. We report coarse-grain force field parameters for N-lignoceryl sphingosine (ceramide NS, also known as ceramide 2) that are consistent with the Martini force field. These parameters were optimized for simulations in the gel phase and validated against atomistic simulations. Coarse-grained simulations with our parameters provide areas per lipid, membrane thicknesses, and electron density profiles that are in good agreement with atomistic simulations.

Molecular Dynamics

Full Kinetics of CO Entry, Internal Diffusion, and Exit in Myoglobin from Transition-Path Theory Simulations

Tang-Qing Yu, Mauro Lapelosa, Eric Vanden-Eijnden, Cameron F. Abrams [Drexel University]

J. Am. Chem. Soc., **137**, 3041–3050, 2015.

We use Markovian milestoning molecular dynamics (MD) simulations on a tessellation of the collective variable space for CO localization in myoglobin to estimate the kinetics of entry, exit, and internal site-hopping. The tessellation is determined by analysis of the free-energy surface in that space using transition-path theory (TPT), which provides criteria for defining optimal milestones, allowing short, independent, cell-constrained MD simulations to provide properly weighted kinetic data.

Internal coordinate density of state from molecular dynamics simulation

Pin-Kuang Lai, Shiang-Tai Lin [National Taiwan University]

J. Comp. Chem., **36**, 507–517, 2015.

The vibrational density of states (DoS), calculated from the Fourier transform of the velocity autocorrelation function, provides profound information regarding the structure and dynamic behavior of a system. However, it is often difficult to identify the exact vibrational mode associated with a specific frequency if the DoS is determined based on velocities in Cartesian coordinates. Here, the DoS is determined based on velocities in internal coordinates, calculated from Cartesian atomic velocities using a generalized Wilson's B-matrix.

Dynamics and Mechanism of UV-Damaged DNA Repair in Indole–Thymine Dimer Adduct: Molecular Origin of Low Repair Quantum Efficiency

Xunmin Guo, Zheyun Liu, Qinhua Song, Lijuan Wang, Dongping Zhong [The Ohio State University]

J. Phys. Chem. B., **119**, 3446–3455, 2015.

Many biomimetic chemical systems for repair of UV-damaged DNA showed very low repair efficiency, and the molecular origin is still unknown. Here, we report our systematic characterization of the repair dynamics of a model compound of indole–thymine dimer adduct in three solvents with different polarity. By resolving all elementary steps including three electron-transfer processes and two bond-breaking and bond-formation dynamics with femtosecond resolution, we observed the slow electron injection in 580 ps in water, 4 ns in acetonitrile, and 1.38 ns in dioxane, the fast back electron transfer without repair in 120, 150, and 180 ps, and the slow bond splitting in 550 ps, 1.9 ns, and 4.5 ns, respectively.

QM and QM/MM

Quantum Chemistry Calculation-Aided Structural Optimization of Combretastatin A-4-like Tubulin Polymerization Inhibitors: Improved Stability and Biological Activity

Junhang Jiang, Canhui Zheng, Kongkai Zhu, Jia Liu, Nannan Sun, Chongqing Wang, Hualiang Jiang, Ju Zhu, Cheng Luo, Youjun Zhou [Second Military Medical University]

J. Med. Chem., **58**, 2538–2546, 2015.

A potent combretastatin A-4 (CA-4) like tubulin polymerization inhibitor 22b was found with strong antitumor activity previously. However, it easily undergoes cis–trans isomerization under natural light, and the resulting decrease in activity limits its further applications. In this study, we used quantum chemistry calculations to explore the molecular basis of its instability. Aided by the calculations, two rounds of structural optimization of 22b were conducted. Accelerated quantitative light stability testing confirmed that the stability of these designed compounds was significantly improved as predicted.

QM and QM/MM (Cont'd)

New insights into steric and electronic effects in a series of phosphine ligands from the perspective of local quantum similarity using the Fukui function

Alejandro Morales-Bayuelo [Universidad de Talca] , Julio Caballero

J. Mol.Mod., **21**, 45, 2015.

The field of molecular quantum similarity (MQS) was introduced by Carbó-Dorca 30 years ago. MQS currently suffers from numerous bottlenecks, for example when studying similarities in chemical reactivity, because there is no clear guidance on the best methodology to follow. For this reason, we have revisited this topic here. Today's search tools and methodologies have made an important contribution to studying steric and electronic effects in phosphine ligands (PR3). In this contribution, we propose a hybrid methodology joining (MQS) and chemical reactivity.

Coupled-Cluster Studies of Extensive Green Fluorescent Protein Models Using the Reduced Virtual Space Approach

Robert Send, Carl-Mikael Suomivuori, Ville R. I. Kaila, Dage Sundholm [University of Helsinki]

J. Phys. Chem. B., **119**, 2933–2945, 2015.

Accurate predictions of photoexcitation properties are a major challenge for modern methods of theoretical chemistry. We show here how approximate coupled-cluster singles and doubles (CC2) calculations in combination with the reduced virtual space (RVS) approach can be employed in studies of excited states of large biomolecular systems. The RVS-CC2 approach is used for accurately predicting optical properties of the p-hydroxybenzylidene-dihydroimidazolinone (p-HBDI) chromophore embedded in green fluorescent protein (GFP) models using quantum mechanical calculations in combination with large basis sets.

Photophysical and Quantum Chemical Studies on the Interactions of Oxazine-1 Dye with Cucurbituril Macrocycles

Mhejabeen Sayed, Mahesh Sundararajan, Jyotirmayee Mohanty[Bhabha Atomic Research Centre], Achikanath C. Bhasikuttan, Haridas Pal

J. Phys. Chem. B., **119**, 3046–3057, 2015.

Supramolecular host–guest interaction of cationic oxazine-1 (OX1) dye with two cucurbit[n]uril (CBn) hosts, namely, CB7 and CB8, has been investigated using photophysical and quantum chemical studies. Both CB7 and CB8 display much stronger binding affinities for OX1 dye compared to conventional cyclodextrin (CD) hosts, which arises due to strong ion–dipole interaction in stabilizing the dye–host inclusion complexes in the present systems. From photophysical studies supported by 1H NMR results and quantum chemical calculations, it is inferred that 1:1 inclusion complexes are mainly formed in the present systems, though a small percentage of 1:2 (dye•host2) complexes are also indicated from time-resolved (TR) fluorescence studies.

Electronic Circular Dichroism of Fluorescent Proteins: A Computational Study

Anna Pikulska, Arnfinn Hykkerud Steindal, Maarten T. P. Beerepoot, Magdalena Pecul [University of Tromsø–The Arctic University of Norway]

J. Phys. Chem. B., **119**, 3377–3386, 2015.

The electronic circular dichroism (ECD) properties of the green fluorescent protein and other fluorescent proteins have been calculated with density functional theory. The influence of different embedding models on the ECD signal of the chromophore has been investigated by modeling the protein environment by the polarizable continuum model (QM/PCM), by the polarizable embedding model (PE-QM/MM), by treating the minimal environment quantum mechanically at the same footing as the chromophore (QM/QM), and by adding the remaining part of the protein by means of PCM (QM/QM/PCM).

QM and QM/MM (Cont'd)

⁷⁷Se Chemical Shift Tensor of L-Selenocystine: Experimental NMR Measurements and Quantum Chemical Investigations of Structural Effects

Jochem Struppe, Yong Zhang [University of Delaware], Sharon Rozovsky

J. Phys. Chem. B., **119**, 3643–3650, 2015.

The genetically encoded amino acid selenocysteine and its dimeric form, selenocystine, are both utilized by nature. They are found in active sites of selenoproteins, enzymes that facilitate a diverse range of reactions, including the detoxification of reactive oxygen species and regulation of redox pathways. Due to selenocysteine and selenocystine's specialized biological roles, it is of interest to examine their ⁷⁷Se NMR properties and how those can in turn be employed to study biological systems. We report the solid-state ⁷⁷Se NMR measurements of the L-selenocystine chemical shift tensor, which provides the first experimental chemical shift tensor information on selenocysteine-containing systems.

Influence of Base Stacking Geometry on the Nature of Excited States in G-Quadruplexes: A Time-Dependent DFT Study

Christopher J. Lech, Anh Tuân Phan, Maria-Elisabeth Michel-Beyerle, Alexander A. Voityuk [Institució Catalana de Recerca i Estudis Avançats (ICREA)]

J. Phys. Chem. B., **119**, 3697–3705, 2015.

G-quadruplexes are four-stranded structures of nucleic acids that are formed from the association of guanine nucleobases into cyclical arrangements known as tetrads. G-quadruplexes are involved in a host of biological processes and are of interest in nanomaterial applications. However, not much is known about their electronic properties. In this paper, we analyze electronic excited states of G-quadruplexes using a combination of time-dependent DFT calculations and molecular dynamics simulations. We systematically consider experimentally observed arrangements of stacked guanine tetrads.

Glutathione as a Prebiotic Answer to α -Peptide Based Life

Béla Fiser, Balázs Jójárt, Milán Szőri, György Lendvay, Imre G. Csizmadia, Béla Viskolcz [University of Szeged]

J. Phys. Chem. B., **119**, 3940–3947, 2015.

The energetics of peptide bond formation is an important factor not only in the design of chemical peptide synthesis, but it also has a role in protein biosynthesis. In this work, quantum chemical calculations at 10 different levels of theory including G3MP2B3 were performed on the energetics of glutathione formation. The strength of the peptide bond is found to be closely related to the acid strength of the to-be N-terminal and the basicity of the to-be C-terminal amino acid. It is shown that the formation of the first peptide activates the amino acid for the next condensation step, manifested in bacterial protein synthesis where the first step is the formation of an N-formylmethionine dipeptide.

QM and QM/MM (Cont'd)

Theoretical studies on the deacylation step of acylated *Candida Antarctica* lipase B: Structural and reaction pathway analysis

Mohammad Sadegh Sadeghi Googheri [Ferdowsi University of Mashhad], Mohammad Reza Housaindokht, Hassan Sabzyan

J. Mol. Graph. and Mod., **57**, 9-19, 2015.

The deacylation step of acylated *Candida Antarctica* lipase B, which was acylated with methylcaprylate (MEC) and acetylcholine (ACh), has been studied by using density functional theory method. Free energies of the entire reaction were calculated for enzyme deacylation by water and hydrogen peroxide that represented hydrolysis and perhydrolysis reactions, respectively. The calculations displayed that a stepwise mechanism there was with the enzyme-product complex being a deep minimum on the free energy surfaces of both of two reactions. The tetrahedral intermediate formation was the rate-determining step of all reactions, which needed 8.1 to 10.5 kcal mol⁻¹ for activation in different reactions.

QM/MM Investigation of ATP Hydrolysis in Aqueous Solution

Cui Wang, Wenting Huang, Jie-Lou Liao [University of Science and Technology of China]

J. Phys. Chem. B., **119**, 3720–3726, 2015.

Adenosine-5'-triphosphate (ATP) hydrolysis represents a most important reaction in biology. Despite extensive research efforts, the mechanism for ATP hydrolysis in aqueous solution still remains under debate. Previous theoretical studies often predefined reaction coordinates to characterize the mechanism for ATP hydrolysis in water with Mg²⁺ by evaluating free energy profiles through these preassumed reaction paths. In the present work, a nudged elastic band method is applied to identify the minimum energy path calculated with a hybrid quantum mechanics and molecular mechanics approach.

Simulating the Distance Distribution between Spin-Labels Attached to Proteins

Shahidul M. Islam, Benoît Roux [University of Chicago]

J. Phys. Chem. B., **119**, 3901–3911, 2015.

EPR/DEER spectroscopy is playing an increasingly important role in the characterization of the conformational states of proteins. In this study, force field parameters for the bifunctional spin-label (RX) used in EPR/DEER are parametrized and tested with molecular dynamics (MD) simulations. The dihedral angles connecting the C α atom of the backbone to the nitroxide ring moiety of the RX spin-label attached to *i* and *i* + 4 positions in a polyalanine α -helix agree very well with those observed in the X-ray crystallography. Both RX_{*i,i*+4} and RX_{*i,i*+3} are more rigid than the monofunctional spin-label (R1) commonly used in EPR/DEER, while RX_{*i,i*+4} is more rigid and causes less distortion in a protein backbone than RX_{*i,i*+3}.

Ligand Docking

Computational and Functional Analyses of a Small-Molecule Binding Site in ROMK

Daniel R. Swale, Jonathan H. Sheehan, Sreedatta Banerjee, Afeef S. Husni, Thuy T. Nguyen, Jens Meiler, Jerod S. Denton [Vanderbilt University Medical Center]

Biophysical Journal. **108**, 1094-1103, 2015.

The renal outer medullary potassium channel (ROMK, or Kir1.1, encoded by *KCNJ1*) critically regulates renal tubule electrolyte and water transport and hence blood volume and pressure. The discovery of loss-of-function mutations in *KCNJ1* underlying renal salt and water wasting and lower blood pressure has sparked interest in developing new classes of antihypertensive diuretics targeting ROMK. Cluster analysis of 2498 low-energy poses resulting from 9900 Monte Carlo docking trajectories on each of 10 conformationally distinct ROMK comparative homology models identified two putative binding sites in the transmembrane pore that were subsequently tested for a role in VU591-dependent inhibition using site-directed mutagenesis and patch-clamp electrophysiology.

Identification of chikungunya virus nsP2 protease inhibitors using structure-base approaches

Phuong T.V. Nguyen, Haibo Yu, Paul A. Keller[University of Wollongong]

J. Mol.Graph. and Mod., **57**, 1-8,2015.

The nsP2 protease of chikungunya virus (CHIKV) is one of the essential components of viral replication and it plays a crucial role in the cleavage of polyprotein precursors for the viral replication process. Therefore, it is gaining attention as a potential drug design target against CHIKV. Based on the recently determined crystal structure of the nsP2 protease of CHIKV, this study identified potential inhibitors of the virus using structure-based approaches with a combination of molecular docking, virtual screening and MD simulations. The top hit compounds from database searching, using the NCI Diversity Set II, with targeting at five potential binding sites of the nsP2 protease, were identified by blind dockings and focused dockings.

Characterization of ICAM-1 biophore to design cytoadherence blocking peptides

A. Mehra, Gaurav Jerath, Vibin Ramakrishnan, Vishal Trivedi[Indian Institute of Technology-Guwahati]

J. Mol.Graph. and Mod., **57**, 27-35,2015.

Peptides from natural sources are good starting material to design bioactive agents with desired therapeutic property. IB peptide derived from the ICAM-1 has been studied extensively as an agent to disrupt the non-specific binding of lymphocyte to the endothelial cells. ICAM-1: IB molecular model reveals that IB peptide binds in an extended conformation to the ICAM-1, masking LFA-1 and partially covering PfEMP-1 binding site. Considering the regioselective requirement of ICAM-1: PfEMP1 binding site, IB peptide charge and 3-D conformation are optimized through generation of combinatorial peptide library containing single, double, triple, tetra and quadra amino acid substitutions of IB peptide.

Ligand Docking (Cont'd)

Comparing sixteen scoring functions for predicting biological activities of ligands for protein targets

Weijun Xu, Andrew J. Lucke, David P. Fairlie [The University of Queensland]

J. Mol. Graph. and Mod., **57**, 76-88, 2015.

Accurately predicting relative binding affinities and biological potencies for ligands that interact with proteins remains a significant challenge for computational chemists. Most evaluations of docking and scoring algorithms have focused on enhancing ligand affinity for a protein by optimizing docking poses and enrichment factors during virtual screening. However, there is still relatively limited information on the accuracy of commercially available docking and scoring software programs for correctly predicting binding affinities and biological activities of structurally related inhibitors of different enzyme classes

PENG: A Neural Gas-Based Approach for Pharmacophore Elucidation. Method Design, Validation, and Virtual Screening for Novel Ligands of LTA4H

Daniel Moser, Sandra K. Wittmann, Jan Kramer, René Blöcher, Janosch Achenbach, Denys Pogoryelov, Ewgenij Proschak [Goethe University]

J. Chem. Infor. and Mod. **55**, 284–293, 2015.

The pharmacophore concept is commonly employed in virtual screening for hit identification. A pharmacophore is generally defined as the three-dimensional arrangement of the structural and physicochemical features of a compound responsible for its affinity to a pharmacological target. Given a number of active ligands binding to a particular target in the same manner, it can reasonably be assumed that they have some shared features, a common pharmacophore. We present a growing neural gas (GNG)-based approach for the extraction of the relevant features which we called PENG (pharmacophore elucidation by neural gas). Results of retrospective validation indicate an acceptable quality of the generated models.

Role of Water in Ligand Binding to Maltose-Binding Protein: Insight from a New Docking Protocol Based on the 3D-RISM-KH Molecular Theory of Solvation

WenJuan Huang, Nikolay Blinov, David S. Wishart, Andriy Kovalenko [University of Alberta]

J. Chem. Infor. and Mod. **55**, 317–328, 2015.

Maltose-binding protein is a periplasmic binding protein responsible for transport of maltooligosaccharides through the periplasmic space of Gram-negative bacteria, as a part of the ABC transport system. The molecular mechanisms of the initial ligand binding and induced large scale motion of the protein's domains still remain elusive. In this study, we use a new docking protocol that combines a recently proposed explicit water placement algorithm based on the 3D-RISM-KH molecular theory of solvation and conventional docking software (AutoDock Vina) to explain the mechanisms of maltotriose binding to the apo-open state of a maltose-binding protein.

A Collective Variable for the Rapid Exploration of Protein Druggability

Rémi Cuchillo, Kevin Pinto-Gil, Julien Michel [Joseph Black Building]

J. Chem. Theor. and Comp. **11**, 1292–1307, 2015.

An efficient molecular simulation methodology has been developed for the evaluation of the druggability (ligandability) of a protein. Previously proposed techniques were designed to assess the druggability of crystallographic structures and cannot be tightly coupled to molecular dynamics (MD) simulations. By contrast, the present approach, JEDI (JustExploring Druggability at protein Interfaces), features a druggability potential made of a combination of empirical descriptors that can be collected “on-the-fly” during MD simulations.

Ligand Docking (Cont'd)

Toward Understanding Allosteric Activation of Thrombin: A Conjecture for Important Roles of Unbound Na⁺ Molecules around Thrombin

Ikuo Kurisaki, Masayoshi Takayanagi, Masataka Nagaoka
[Nagoya University]

J. Phys. Chem. B., **119**, 3635–3642, 2015.

We shed light on important roles of unbound Na⁺ molecules in enzymatic activation of thrombin. Molecular mechanism of Na⁺-activation of thrombin has been discussed in the context of allostery. However, the recent challenge to redesign K⁺-activated thrombin revealed that the allosteric interaction is insufficient to explain the mechanism. Under these circumstances, we have examined the roles of unbound Na⁺ molecule in maximization of thrombin-substrate association reaction rate. We performed all-atomic molecular dynamics (MD) simulations of thrombin in the presence of three different cations; Li⁺, Na⁺, and Cs⁺.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 57, April, 2015.

- 1-8 **Identification of chikungunya virus nsP2 protease inhibitors using structure-base approaches** ,Phuong T.V. Nguyen, Haibo Yu, Paul A. Keller[University of Wollongong]

See Methodology / Ligand Docking.

- 9-19 **Theoretical studies on the deacylation step of acylated Candida Antarctica lipase B: Structural and reaction pathway analysis** ,Mohammad Sadegh Sadeghi Googheri [Ferdowsi University of Mashhad], Mohammad Reza Housaindokht, Hassan Sabzyan

See Methodology / QM and QM/MM.

- 20-26 **Dissipative particle dynamics study on self-assembled platycodin structures: The potential biocarriers for drug delivery** ,Xingxing Dai, Haiou Ding, Qianqian Yin, Guang Wan, Xinyuan Shi[Beijing University of Chinese Medicine], Yanjiang Qiao

See Applications / Medicinal Chemistry and Drug Design.

- 27-35 **Characterization of ICAM-1 biophore to design cytoadherence blocking peptides** ,A. Mehra, Gaurav Jerath, Vibin Ramakrishnan, Vishal Trivedi[Indian Institute of Technology-Guwahati]

See Methodology / Ligand Docking.

- 36-48 **Can structural features of kinase receptors provide clues on selectivity and inhibition? A molecular modeling study** ,Sarangan Ravichandran [Frederick National Laboratory for Cancer Research (FNLRCR)], Brian T. Luke, Jack R. Collins

See Applications / Medicinal Chemistry and Drug Design.

- 49-61 **Molecular recognition of avirulence protein (avrxa5) by eukaryotic transcription factor xa5 of rice (Oryza sativa L.): Insights from molecular dynamics simulations** ,Budheswar Dehury, Jitendra Maharana, Bikash Ranjan Sahoo, Jagajjit Sahu, Priyabrata Sen, Mahendra Kumar Modi, Madhumita Barooah[Assam Agricultural University]

See Applications / Protein- Protein Interaction.

- 62-69 **Computational study of diketopyrrolopyrrole-based organic dyes for dye sensitized solar cell applications** ,Wenjie Fan [Liaoning University of Technology], Dazhi Tan, Qijian Zhang, Huaxing Wang

Four diketopyrrolopyrrole (DPP)-based organic dyes utilizing the donor- π -acceptor motif were investigated by density functional theory (DFT) and time-dependent DFT (TDDFT) approaches. The four dyes were composed of different donor groups, i.e. indoline, carbazole, triphenylamine, and coumarin.

- 70-75 **Removal of trihalomethanes from aqueous solution through armchair carbon nanotubes: A molecular dynamics study** ,Jafar Azamat, Alireza Khataee [University of Tabriz], Sang Woo Joo, Binfeng Yin

See Applications / Carbon Nanotubes.

- 76-88 **Comparing sixteen scoring functions for predicting biological activities of ligands for protein targets** ,Weijun Xu, Andrew J. Lucke, David P. Fairlie[The University of Queensland]

See Methodology / Ligand Docking.

- 89-98 **Structure based virtual screening to identify selective phosphodiesterase 4B inhibitors** ,Rahul P. Gangwal, Mangesh V. Damre, Nihar R. Das, Gaurao V. Dhoke, Anuseema Bhadauriya, Rohith A. Varikoti, Shyam S. Sharma, Abhay T. Sangamwar[National Institute of Pharmaceutical Education and Research (NIPER)]

See Applications / Enzyme Catalysis.

- 99-105 **Mutual influence between anion- π and pnictogen bond interactions: The enhancement of P $\cdots$ N and P $\cdots$ O interactions by an anion- π bond** ,Mehdi D. Esrafil [University of Maragheh], Fariba Mohammadian-Sabet, Mohammad Solimannejad

In this work, the interplay between anion- π and pnictogen bond interactions is investigated by ab initio calculations. Cooperative effects are observed in the studied complexes in which anion- π and pnictogen bond interactions coexist. These effects are analyzed in detail in terms of the energetic, geometric, charge-transfer and electron density properties of the complexes.

- 106-113 **Local elastic constants of LacI and implications for allostery** ,Andre A.S.T. Ribeiro, Vanessa Ortiz[Columbia University]

See Applications / Protein Dynamics.

- 114-121 **Molecular dynamics simulations to calculate glass transition temperature and elastic constants of novel polyethers** ,Radhakrishnan Sarangapani [High Energy Materials Research Laboratory], Sreekantha T. Reddy, Arun K. Sikder

Molecular dynamics simulations studies are carried out on hydroxyl terminated polyethers that are useful in energetic polymeric binder applications.

- 122-130 **Molecular modeling and identification of novel glucokinase activators through stepwise virtual screening** ,Pabitra Mohan Behera, Deepak Kumar Behera, Suresh Satpati, Geetanjali Agnihotri, Sanghamitra Nayak, Payodhar Padhi, Anshuman Dixit[Institute of Life Sciences, Nalco Square, Bhubaneswar]

See Applications / Enzyme Catalysis.

- 131-142 **Human PD-1 binds differently to its human ligands: A comprehensive modeling study** ,Clement Viricel, Marawan Ahmed, Khaled Barakat[University of Alberta]

See Applications / Ligand Binding.

- 143-155 **Molecular modeling and docking study on dopamine D2-like and serotonin 5-HT2A receptors** ,Xinli Duan, Min Zhang, Xin Zhang, Fang Wang, Ming Lei[Beijing University of Chemical Technology]

See Applications / Homology Modeling.

Journal of Computational Chemistry, 36 (6), March, 2015.

- 355–360 **Pentaatomic planar tetracoordinate silicon with 14 valence electrons: A large-scale global search of SiX_nY_m ($n + m = 4$; $q = 0, \pm 1, -2$; X, Y = main group elements from H to Br)** ,Jing Xu , Yi-hong Ding[Jilin University]

Designing and characterizing the compounds with exotic structures and bonding that seemingly contrast the traditional chemical rules are a never-ending goal. Although the silicon chemistry is dominated by the tetrahedral picture, many examples with the planar tetracoordinate-Si skeletons have been discovered, among which simple species usually contain the 17/18 valence electrons.

- 361–375 **Assessment of hydrophobic interactions and their contributions through the analysis of the methane dimer** ,V́ctor Duarte Alaniz, Tomás Rocha-Rinza[Universidad Nacional Aut́noma de Ḿxico] , Gabriel Cuevas

Hydrophobic Interactions (HIs) are important in many phenomena of molecular recognition in chemistry and biology. Still, the relevance of HIs is sometimes difficult to evaluate particularly in large systems and intramolecular interactions. We put forward a method to estimate the magnitude and the different contributions of a given HI of the $\text{C}\cdots\text{C}$, $\text{H C}\cdots\text{H}$, and $\text{H}\cdots\text{H}$ type.

- 376–384 **Force field development for organic molecules: Modifying dihedral and 1–n pair interaction parameters** ,Siyan Chen, Shasha Yi, Wenmei Gao, Chunheng Zuo , Zhonghan Hu [Jilin University]

We comprehensively illustrate a general process of fitting all-atom molecular mechanics force field (FF) parameters based on quantum mechanical calculations and experimental thermodynamic data.

- 385–391 **Search for the global minimum structures of AlB₃H₂n (n = 0 – 6) clusters** ,İskender Muz, Osman Canko [Nevsehir Hacı Bektas Veli University], Murat Atiş , Erdem Kamil Yıldırım

The global minimum structures of AlB₃H₂n (n = 0–6) clusters are determined using the stochastic search method at the B3LYP/6–31G level of theory. These initially specified geometries are recalculated using B3LYP and CCSD(T) methods using the 6–311++G** basis set.

- 392–398 **An incremental isoconversional method for kinetic analysis based on the orthogonal distance regression** ,Tibor Dubaj [Slovak University of Technology], Zuzana Cibulková ,Peter Šimon

The parameters obtained from a kinetic analysis of thermoanalytical data often exhibit a conversion-dependent behavior. A novel incremental isoconversional method able to deal with this phenomenon is proposed.

- 399–407 **Essential dynamics for the study of microstructures in liquids** ,Maira D'Alessando, Andrea Amadei, Mauro Stener , Massimiliano Aschi [Universita' di l'Aquila]

See Applications / Protein Dynamics.

- 408–422 **Persistent homology for the quantitative prediction of fullerene stability** ,Kelin Xia, Xin Feng, Yiyong Tong[Michigan State University] , Guo Wei Wei

Persistent homology is a relatively new tool often used for qualitative analysis of intrinsic topological features in images and data originated from scientific and engineering applications. In this article, we report novel quantitative predictions of the energy and stability of fullerene molecules, the very first attempt in using persistent homology in this context.

Journal of Computational Chemistry, 36 (7), March, 2015.

- 424–432 **New insights into the meaning and usefulness of principal component analysis of concatenated trajectories** ,Gustavo Pierdominici-Sottile , Juliana Palma [Universidad Nacional de Quilmes]

A comparison between different conformations of a given protein, relating both structure and dynamics, can be performed in terms of combined principal component analysis (combined-PCA). To that end, a trajectory is obtained by concatenating molecular dynamics trajectories of the individual conformations under comparison.

- 433–440 **H₂ adsorption on Ag-nanocluster/single-walled carbon nanotube composites: A molecular dynamics study on the effects of nanocluster size, diameter, and chirality of nanotube** ,Hamed Akbarzadeh [Hakim Sabzevari University], Amir Nasser Shamkhali

See Applications / Carbon Nanotubes.

- 441–448 **Application of polarizable ellipsoidal force field model to pnictogen bonds** ,Fang Liu, Likai Du [Chinese Academy of Sciences], Jun Gao, Lili Wang, Bo Song , Chengbu Liu

Noncovalent interactions, such as hydrogen bonds and halogen bonds, are frequently used in drug designing and crystal engineering. To understand the anisotropic characters of pnictogen bond, a modification of the polarizable ellipsoidal force field (PEff) model previously used to define halogen bonds was proposed in this work.

- 449–458 **Ionic bonding of lanthanides, as influenced by d- and f-atomic orbitals, by core–shells and by relativity** ,Wen-Xin Ji, Wei Xu, W. H. Eugen Schwarz , Shu-Guang Wang [Shanghai Jiao Tong University]

Lanthanide trihalide molecules LnX_3 ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$) were quantum chemically investigated, in particular detail for $\text{Ln} = \text{Lu}$ (lutetium). We applied density functional theory (DFT) at the nonrelativistic and scalar and SO-coupled relativistic levels, and also the ab initio coupled cluster approach.

- 459–466 **Theoretical investigation of enantioselectivity of cage-like supramolecular assembly: The insights into the shape complementarity and host–guest interaction** ,Yusuke Ootani, Yoshinobu Akinaga , Takahito Nakajima [Advanced Institute for Computational Science, Chuo]

Enantioselectivity in the aza-Cope rearrangement of a guest molecule encapsulated in a cage-like supramolecular assembly $[\text{Ga}_4\text{L}_6]^{12-}$ [$\text{L} = 1,5\text{-bis}(2',3'\text{-dihydroxybenzamido})\text{naphthalene}$] is investigated using density functional theory and ab initio molecular orbital calculations. Reaction pathways leading to R- and S-enantiomers encapsulated in the $[\text{Ga}_4\text{L}_6]^{12-}$ are explored.

- 467–477 **STOCK: Structure mapper and online coarse-graining kit for molecular simulations** ,Staš Bevc [National Institute of Chemistry, Ljubljana], Christoph Junghans , Matej Praprotnik

See Applications / Bioinformatics.

- 478–492 **The development of an artificial organic networks toolkit for LabVIEW** ,Hiram Ponce [Universidad Panamericana], Pedro Ponce , Arturo Molina

Two of the most challenging problems that scientists and researchers face when they want to experiment with new cutting-edge algorithms are the time-consuming for encoding and the difficulties for linking them with other technologies and devices. In that sense, this article introduces the artificial organic networks toolkit for LabVIEW™ (AON-TL) from the implementation point of view.

Journal of Computational Chemistry, 36 (8), March, 2015.

- 493–506 **k-Nearest neighbors optimization-based outlier removal** ,Abraham Yosipof , Hanoch Senderowitz [Bar Ilan University]

Datasets of molecular compounds often contain outliers, that is, compounds which are different from the rest of the dataset. Outliers, while often interesting may affect data interpretation, model generation, and decisions making, and therefore, should be removed from the dataset prior to modeling efforts. Here, we describe a new method for the iterative identification and removal of outliers based on a k-nearest neighbors optimization algorithm.

- 507–517 **Internal coordinate density of state from molecular dynamics simulation** ,Pin-Kuang Lai ,Shiang-Tai Lin[National Taiwan University]

See Methodology / Molecular Dynamics.

- 518–528 **Theoretical prediction of the host–guest interactions between novel photoresponsive nanorings and C60: A strategy for facile encapsulation and release of fullerene** ,Kun Yuan, Jing-Shuang Dang, Yi-Jun Guo , Xiang Zhao [Xi'an Jiaotong University]

See Applications / Host-Guest Systems.

- 529–538 **Energy decomposition analysis of cation– π , metal ion–lone pair, hydrogen bonded, charge-assisted hydrogen bonded, and π – π interactions** ,Bhaskar Sharma, Hemant Kumar Srivastava, Gaddamanugu Gayatri , Garikapati Narahari Sastry [CSIR-Indian Institute of Chemical Technology]

This study probes the nature of noncovalent interactions, such as cation– π , metal ion–lone pair (M–LP), hydrogen bonding (HB), charge-assisted hydrogen bonding (CAHB), and π – π interactions, using energy decomposition schemes—density functional theory (DFT)—symmetry-adapted perturbation theory and reduced variational space.

- 539–552 **Prediction of the structures of helical membrane proteins based on a minimum unfavorable contacts approach** ,Siladitya Padhi, Siddabattula Ramakrishna , U. Deva Priyakumar[International Institute of Information Technology, Hyderabad]

See Applications / Protein Structure Analysis.

- 553–563 **MetREx: A protein design approach for the exploration of sequence-reactivity relationships in metalloenzymes** ,Martin T. Stiebritz [Laboratorium für Physikalische Chemie, ETH Zürich]

See Applications / Enzyme Catalysis.

- 564–572 **Estimating π binding energy of N-Heterocyclic carbenes: The role of polarization** ,Elixabete Rezabal , Gilles Frison [Ecole Polytechnique and CNRS]

In this work, the tuneability of the π acceptor or donor properties of a set of N-heterocyclic carbenes (NHCs) with a wide spectrum of electronic characteristics is established by means of density functional theory and energy decomposition analysis (EDA) tools.

- 573–583 **Etomica: An object-oriented framework for molecular simulation** ,Andrew J. Schultz , David A. Kofke [The State University of New York]

See Applications / Bioinformatics.

Journal of Molecular Modeling, 21 (3), March, 2015.

- 66 **Water-assisted isomerization of the [H, C, N, O] syste** ,Jia Cao [Yan'an University], Zhi Xiang Wang, Lou Jun Gao, Feng Fu

Ten minima of [H, C, N, O] isomers were investigated in gas phase and water solution using the polarizable continuum model at the CCSD(T)/M06-2X/6-311 + G(3df,2p) level of theory.

- 65 **Does single-electron chalcogen bond exist? Some theoretical insights** ,Mehdi D. Esrafil [University of Maragheh], Fariba Mohammadian-Sabet

Ab initio calculations have been carried out to investigate the σ -hole interaction in $\text{XHY}\cdots\text{CH}_3$ and $\text{XHY}\cdots\text{CH}_2\text{CH}_3$ complexes, where $\text{X} = \text{F}, \text{Cl}, \text{Br}$ and $\text{Y} = \text{S}, \text{Se}$. This interaction, termed "single-electron chalcogen bond interaction" was analyzed in terms of geometric, interaction energies and electronic features of the complexes.

- 64 **Studies of conformational changes of an arginine-binding protein from *Thermotoga maritima* in the presence and absence of ligand via molecular dynamics simulations with the coarse-grained UNRES force field**, Agnieszka G. Lipska, Adam K. Sieradzian, Paweł Krupa, Magdalena A. Mozolewska, Sabato D'Auria, Adam Liwo [University of Gdansk]

See Applications / Protein Confirmation Analysis.

- 63 **Structural prediction of a novel laminarinase from the psychrophilic *Glaciozyma antarctica* PI12 and its temperature adaptation analysis** ,Sepideh Parvizpour [Universiti Teknologi Malaysia], Jafar Razmara, Ashraf Fadhil Jomah, Mohd Shahir Shamsir, Rosli Mohd Illias

See Applications / Homology Modeling.

- 61 **A comparative study of the chalcogen bond, halogen bond and hydrogen bond $\text{S}\cdots\text{O}/\text{Cl}/\text{H}$ formed between SHX and HOCl** ,Yi Fang, An Yong Li [Southwest University], Fei Yan Ma

Ab initio quantum chemistry methods were used to analyze the noncovalent interactions between HOCl and SHX ($\text{X} = \text{F}, \text{CN}, \text{NC}, \text{Cl}, \text{Br}, \text{NO}_2, \text{CCH}, \text{CH}_3, \text{H}$). Three energetic minimal configurations were characterized for each case, where the S center acts as a Lewis acid interacting with O to form a chalcogen bond, as well as a Lewis base interacting with Cl or H of HOCl to form halogen bond and hydrogen bond, respectively.

- 60 **Exploring σ -hole bonding in $\text{XH}_3\text{Si}\cdots\text{HMY}$ ($\text{X} = \text{H}, \text{F}, \text{CN}$; $\text{M} = \text{Be}, \text{Mg}$; $\text{Y} = \text{H}, \text{F}, \text{CH}_3$) complexes: a "tetrel-hydride" interaction** ,Mehdi D. Esrafil [University of Maragheh], Fariba Mohammadian-Sabet

In this work, a σ -hole interaction is predicted theoretically in $\text{XH}_3\text{Si}\cdots\text{HMY}$ complexes, where $\text{X} = \text{H}, \text{F}, \text{CN}$; $\text{M} = \text{Be}, \text{Mg}$ and $\text{Y} = \text{H}, \text{F}, \text{CH}_3$. The properties of this interaction, termed "tetrel-hydride" interaction, are investigated in terms of geometric, interaction energies, and electronic features of the complexes.

- 59 **A polar nature of benzoic acids extrusion from nitroalkyl benzoates: DFT mechanistic study**, Radomir Jasiński [Cracow University of Technology], Agnieszka Kącka

Using DFT calculations at various theory levels, quantum-chemical simulations of decomposition paths were performed for a series of nitroalkyl benzoates. It was discovered, that these reactions proceed via polar, but one-step mechanism.

- 58 **Effect of partial atomic charges on the calculated free energy of solvation of poly(vinyl alcohol) in selected solvents**, Abolfazl Noorjahan, Phillip Choi [University of Alberta]

It is well-known that properties of poly(vinyl alcohol) (PVA) in the pure and solution states depend largely on the hydrogen bonding networks formed. In this work, we calculated the PACs for PVA using a few commonly used population analysis schemes with a hope to identify an accurate set of PACs for PVA monomers.

- 57 **The DFT study on the reaction between benzaldehyde and 4-amine-4H-1,2,4-triazole and their derivatives as a source of stable hemiaminals and schiff bases. Effect of substitution and solvation on the reaction mechanism**, Slawomir Berski, Agnieszka J. Gordon, Leszek Zbigniew Ciunik [University of Wrocław]

Reaction mechanism for the benzaldehyde (ald) and 4-amine-4H-1,2,4-triazole (4at) has been investigated at the DFT (B3LYP)/6-31+G(d) computational level. Three transition states (TS) have been identified. The TS1 corresponds to hydrogen transfer from the NH₂ group to the C=O bond and nucleophilic attack of the carbon atom from the aldehyde group on the nitrogen atom from the NH₂ group in 4at.

- 56 **The structure of adsorbed cyclic chains**, Aleksander Kuriata, Andrzej Sikorski [University of Warsaw]

In order to determine the structure of polymer films formed of cyclic chains (rings) we developed and studied a simple coarse-grained model. Our main goal was to check how the percolation and jamming thresholds in such a system were related to the thresholds obtained for linear flexible chains system, i.e., how the geometry of objects influenced both thresholds.

- 55 **Enantiomeric discrimination of chiral organic salts by chiral aza-15-crown-5 ether with C₁ symmetry: experimental and theoretical approaches**, Safak Özhan Kocakaya, Yilmaz Turgut, Necmettin Pirinçcioğlu [University of Dicle]

The work involves an experimental (1H NMR) and theoretical (MD, MM-PBSA and DFT) investigation of the molecular recognition and discrimination properties of a chiral aza-15-crown-5 against methyl esters of alanine, phenylalanine and valine hydrochloride salts.

- 54 **Analysis of degradation mechanism of disperse orange 25 in supercritical water oxidation using molecular dynamic simulations based on the reactive force field**, Jinli Zhang, Jintao Gu, You Han [Tianjin University], Wei Li, Zhongxue Gan, Junjie Gu

4-[N-(2-cyanoethyl)-N-ethylamino]-4'-nitroazo-benzene (disperse orange 25, DO25) is one of the main components in dyeing wastewater. In this work, supercritical water oxidation (SCWO) process of DO25 has been investigated using the molecular dynamic simulations based on the reactive force field (ReaxFF).

- 53 **On the intrinsic reactivity index for electrophilicity/nucleophilicity responses** ,Eduardo Chamorro [Universidad Andres Bello], Junia Melin

We present a critical discussion related to the recent definition of the intrinsic reactivity index, IRI, (Tetrahedron Lett. 2013, 54, 339-342; Tetrahedron 2013, 69, 4247-4258) formulated to describe both, electrophilicity (charge acceptance) and nucleophilicity (charge donation) reactivities.

- 52 **Mathematical modeling and physical reality in noncovalent interactions** ,Peter Politzer [University of New Orleans], Jane S. Murray, Timothy Clark

The Hellmann-Feynman theorem provides a straightforward interpretation of noncovalent bonding in terms of Coulombic interactions, which encompass polarization (and accordingly include dispersion).

- 51 **Mechanical properties of chiral and achiral silicon carbide nanotubes under oxygen chemisorptions** ,R. Ansari, M. Mirnezhad, M. Hosseinzadeh [University of Guilan]

In this paper, the mechanical properties of fully oxygenated silicon carbide nanotubes (O₂-SiCNTs) are explored using a molecular mechanics model joined with the density functional theory (DFT). The closed-form analytical expressions suggested in this study can easily be adapted for nanotubes with different chiralities.

- 50 **Binding properties of SUMO-interacting motifs (SIMs) in yeast** ,Christophe Jardin, Anselm H. C. Horn, Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

See Applications / Ligand Binding.

- 49 **On the origin of surface imposed anisotropic growth of salicylic and acetylsalicylic acids crystals during droplet evaporation** ,Maciej Przybyłek, Piotr Cysewski, Maciej Pawelec [Nicolaus Copernicus University in Toruń], Dorota Ziółkowska, Mirosław Kobierski

In this paper droplet evaporative crystallization of salicylic acid (SA) and acetylsalicylic acid (ASA) crystals on different surfaces, such as glass, polyvinyl alcohol (PVA), and paraffin was studied. The obtained crystals were analyzed using powder X-ray diffraction (PXRD) technique.

- 48 **Electronic and optical properties of N-doped Bi₂O₃ polymorphs for visible light-induced photocatalysis** ,Fang Wang, Kun Cao, Yi Wu, Greta R. Patzke, Ying Zhou [Southwest Petroleum University]

The effect of N doping on the crystal structure, electronic, and optical properties of α -Bi₂O₃ and β -Bi₂O₃ has been studied in detail based with first principle calculations. The crystallographic features of Bi₂O₃ polymorphs are not substantially changed through N doping

- 47 **N-H...O versus O-H...O: density functional calculation and first principle molecular dynamics study on a quinoline-2-carboxamide N-oxide** ,Aneta Jezierska [University of Wrocław]

N-oxide-type compounds are the object of current research interest due to the presence of resonance-assisted N-H...O hydrogen bonds. Here, the metric and spectroscopic parameters of N-methyl-quinoline-2-carboxamide 1-oxide were computed on the basis of density functional theory and Car-Parrinello molecular dynamics.

- 46 **A density functional theory study of hydrocarbon combustion and synthesis on Ni surfaces** ,Abas Mohsenzadeh, Tobias Richards, Kim Bolton [University of Borås]

Combustion and synthesis of hydrocarbons may occur directly ($\text{CH} \rightarrow \text{C} + \text{H}$ and $\text{CO} \rightarrow \text{C} + \text{O}$) or via a formyl (CHO) intermediate. Density functional theory (DFT) calculations were performed to calculate the activation and reaction energies of these reactions on Ni(111), Ni(110), and Ni(100) surfaces.

- 45 **New insights into steric and electronic effects in a series of phosphine ligands from the perspective of local quantum similarity using the Fukui function**, Alejandro Morales-Bayuelo [Universidad de Talca] , Julio Caballero

See Methodology / QM and QM/MM.

- 44 **Theoretical study of stereoselectivity of the [1 + 2] cycloaddition reaction between (1S,3R,8S)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0,0,1.3]dodec-9-ene and dibromocarbene using density functional theory (DFT) B3LYP/6-31G*(d)** ,Abdellah Zeroual, Ahmed Benharref, Abdeslam El Hajbi [Chouaib Doukkali University]

In this work we used density functional theory (DFT) B3LYP/6-31G*(d) to study the stoichiometric reaction between the product (1S,3R,8S)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0,0,1.3]dodec-9-ene (referred to here as P1) and dibromocarbene.

- 43 **Theoretical investigation of the asymmetric molecular harmonic emission and the attosecond pulse generation** ,Li-Qiang Feng [Liaoning University of Technology], Hang Liu

The harmonic emission of the asymmetric charged molecule HeH_2^+ ion is theoretically investigated by solving the one-dimensional-time-dependent Schrödinger equation.

- 42 **Mono and digallium selenide clusters as potential superhalogens** ,Neelum Seeburrun, Edet F. Archibong, Ponnadurai Ramasami[University of Mauritius]

We present a systematic theoretical study on mono and digallium selenide clusters, Ga_mSe_n ($m = 1, 2$ and $n = 1-4$), along with their negatively and positively charged counterparts. Different theoretical methods, namely density functional theory (DFT), second-order Møller-Plesset perturbation theory (MP2) and coupled cluster singles and doubles, including non-iterative triples [CCSD(T)], were employed in conjunction with the 6-311+G(2df) basis set.

- 41 **Performance of Møller-Plesset second-order perturbation theory and density functional theory in predicting the interaction between stannylenes and aromatic molecules** ,Piotr Matczak [University of Łódź], Sławomir Wojtulewski

The performances of Møller-Plesset second-order perturbation theory (MP2) and density functional theory (DFT) have been assessed for the purposes of investigating the interaction between stannylenes and aromatic molecules.

- 40 **Ordered and layered structure of liquid nitromethane within a graphene bilayer: toward stabilization of energetic materials through nanoscale confinement** ,Yingzhe Liu [Xi'an Modern Chemistry Research Institute], Tao Yu, Weipeng Lai, Ying Kang, Zhongxue Ge

The structural characteristics involving thermal stabilities of liquid nitromethane (NM)—one of the simplest energetic materials—confined within a graphene (GRA) bilayer were investigated by means of all-atom molecular dynamics simulations and density functional theory calculations.

- 39 **Electronic transport properties of BN sheet on adsorption of ammonia (NH₃) gas** ,Anurag Srivastava [CNT Lab, ABV-IIITM], Chetan Bhat, Sumit Kumar Jain, Pankaj Kumar Mishra, Ranjeet Brajpuriya

We report the detection of ammonia gas through electronic and transport properties analysis of boron nitride sheet. The density functional theory (DFT) based ab initio approach has been used to calculate the electronic and transport properties of BN sheet in presence of ammonia gas. Analysis confirms that the band gap of the sheet increases due to presence of ammonia.

- 38 **Theoretical study of interactions between electron-deficient arenes and coinage metal anions** ,Yishan Chen [Qijing Normal University], Fan Wang

The binding behavior of coinage metal anions with some electron-deficient arenes has been investigated by MP2 calculations, and the character of interactions in these complexes has been examined by NBO analysis.

- 37 **Homology modeling and molecular dynamics simulation of N-myristoyltransferase from Plasmodium falciparum: an insight into novel antimalarial drug design** ,Paulomi Paul, Abhishek Chowdhury [Assam University], Anupam Das Talukdar, Manabendra Dutta Choudhury

See Applications / Medicinal Chemmistry and Drug Design.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

Aatto Laaksonen
aatto@mmk.su.se.
Stockholm University,
10691 Stockholm,
Sweden

Abdeslam El Hajbi
a_elhajbi@yahoo.fr
Chouaib Doukkali University,
BP 20, 24000,
El Jadida,
Morocco

Abha Mishra
Indian Institute of Technology
(Banaras Hindu University),
Varanasi 221005,
India

Abhay T. Sangamwar
abhays@niper.ac.in
National Institute of
Pharmaceutical Education and
Research (NIPER),
Sector-67, Mohali 160 062,
Punjab, India

Abhishek Chowdhury,
abhishek@bioinfoas.ac.in
Assam University,
Silchar, Assam, 788011,
India

Adam Liwo
adam@sun1.chem.univ.gda.pl
University of Gdansk,
Wita Stwosza 63,
80-308, Gdańsk,
Poland

Adrian H. Elcock
adrian-elcock@uiowa.edu.
University of Iowa,
Iowa City, Iowa 52242,
United States

Afsaneh Maleki,
maleki.afsaneh@iauo.ac.ir
Islamic Azad University,
Omidiyeh Branch,
Omidiyeh, Khuzestan,
Iran

Alan E. van Giessen
vangiess@mtholyoke.edu.
Mount Holyoke College,
50 College Street, South Hadley,
Massachusetts 01075,
United States

Albert Ardevol,
albert.ardevol@phys.chem.ethz.ch.
USI-Campus,
Via Giuseppe Buffi 13,
C-6900 Lugano,
Switzerland

Alejandro Morales-Bayuelo,
alejandr.morales@uandresbello.edu
u
Universidad de Talca,
2 Norte 685,
Casilla 721, Talca,
Chile

Alexander A. Voityuk
alexander.voityuk@icrea.cat.
Institutió Catalana de Recerca i
Estudis Avançats (ICREA),
Barcelona, Spain; Institute of
Computational Chemistry,
Universitat de Girona, 17071
Girona,
Spain

Alexander D. MacKerell, Jr.
alex@outerbanks.umaryland.edu.
University of Maryland,
Baltimore, Maryland 21201,
United States

Alexander M. Andrianov,
National Academy of Sciences of
Belarus,
Kuprevich Street 5/2,
Minsk 220141,
Republic of Belarus

Alexey V. Onufriev
alexey@cs.vt.edu
Virginia Tech, Blacksburg,
Virginia

Alireza Khataee,
ar_khataee@yahoo.com
University of Tabriz,
51666-14766 Tabriz,
Iran

Amedeo Cafilisch
cafilisch@bioc.uzh.ch
University of Zürich,
Winterthurerstrasse 190,
CH-8057 Zürich,
Switzerland

An Yong Li,
aylifnsy@swu.edu.cn
Southwest University,
Tiansheng Road No.1,
Beibei, 400715, Chongqing,
People's Republic of China

Anders Karlén
anders.karlen@orgfarm.uu.se.
Uppsala University,
Biomedical Centre, Box 574, SE-
751 23 Uppsala,
Sweden

András Perczel
perczel@chem.elte.hu
Eötvös Loránd University,
Pázmány P. sétány 1/A,
Budapest, H-1117
Hungary

Andrey A. Toropov,
andrey.toropov@marionegri.it
IRCCS—Istituto di Ricerche
Farmacologiche Mario Negri,
20156, Via La Masa 19,
Milano, Italy

Andriy Kovalenko
andriy.kovalenko@nrc-cnrc.gc.ca.
University of Alberta,
Edmonton, AB T6G 2G8,
Canada

Andrzej Sikorski
sikorski@chem.uw.edu.pl
University of Warsaw,
Pasteura 1,
02-093, Warsaw,
Poland

Anela Ivanova
aivanova@chem.uni-sofia.bg;
University of Sofia, Faculty of
Chemistry and Pharmacy,
Department of Physical Chemistry,
1 James Bourchier Avenue, 1164
Sofia,
Bulgaria

Aneta Jezierska
aneta.jezierska@chem.uni.wroc.pl
University of Wrocław,
ul. F. Joliot-Curie 14,
50-383, Wrocław,
Poland

Anil K. Mishra
Institute of Nuclear Medicine and
Allied Sciences,
Brig. S. K. Mazumdar Road,
Delhi 110054,
India

Anirban Hazra
ahazra@iiserpune.ac.in.
Indian Institute of Science
Education and Research,
Dr. Homi Bhabha Road
Pune, Maharashtra 411 008,
India

Anna Linusson
anna.linusson@chem.umu.se
Umeå University,
90187, Umeå,
Sweden

Anshuman Dixit
anshumandixit@gmail.com
Institute of Life Sciences, Nalco
Square, Bhubaneswar,
751023, Odisha,
India

Anurag Srivastava,
profanurag@gmail.com
Advanced Material Research
Group,
CNT Lab, ABV-IIITM,
Gwalior, M.P.,
India

Arieh Warshel
warshel@usc.edu.
University of Southern California,
3620 McClintock Avenue,
Los Angeles, California 90089,
United States

Béla Viskolcz
viskolcz@jgypk.u-szeged.hu.
University of Szeged,
Boldogasszony sgt. 6,
Szeged, Hungary-6725

Benoît Roux
roux@uchicago.edu.
University of Chicago,
Chicago, Illinois 60637,
United States

Berend Smit
Berend-Smit@berkeley.edu
Institut des Sciences et Ingénierie
Chimiques (ISIC),
Valais, Ecole Polytechnique
Fédérale de Lausanne (EPFL),
Rue de l'Industrie 17
CH-1950 Sion,
Switzerland

Boris Schmidt
schmidt_boris@t-online.de.
Technische Universität Darmstadt,
Alarich-Weiss-Strasse 4,

64287 Darmstadt, Germany	Avenida República 275, 8370146, Santiago, Chile	220 Handan Road, Shanghai 200433, China	Academy of Sciences of the Czech Republic, Královopolská 135, 612 65 Brno, Czech Republic
Cameron F. Abrams cfa22@drexel.edu Drexel University, Philadelphia, Pennsylvania 19104, United States	Eudes Eterno Fileti fileti@gmail.com. Universidade Federal de São Paulo, 12247-014, São José dos Campos, SP, Brazil	Habibah A Wahab habibahw@usm.my. Universiti Sains Malaysia, 11800, Penang, Malaysia	Jeffrey Skolnick skolnick@gatech.edu Center for the Study of Systems Biology, School of Biology, Georgia Institute of Technology, Atlanta, GA 30076, USA
D. Jeya Sundara Sharmila Karunya Univesity, Karunya Nagar, Coimbatore 641114, Tamil Nadu, India	Ewa Rogalska ewa.rogalska@univ-lorraine.fr. CNRS/Université de Lorraine, 54506 Vandoeuvre-lès-Nancy Cedex, France	Hamed Akbarzadeh akbarzadehhamed@yahoo.com Hakim Sabzevari University, Sabzevar, Iran	Jerod S. Denton jerod.s.denton@vanderbilt.edu Vanderbilt University Medical Center, Nashville, Tennessee
Dage Sundholm sundholm@chem.helsinki.fi. University of Helsinki, P.O. Box 55 (A. I. Virtanens plats 1), FI-00014 Helsinki, Finland	Ewgenij Proschak proschak@pharmchem.uni- frankfurt.de. Goethe University, 60438 Frankfurt, Germany	Hanoch Senderowitz hsenderowitz@gmail.com Bar Ilan University, Ramat-Gan, Israel	Jia Cao caojia213@126.com Yan'an University, Shaanxi, 716000, China
David A. Kofke kofke@buffalo.edu University at Buffalo, The State University of New York, Buffalo, New York	Francesca Fanelli fanelli@unimo.it University of Modena and Reggio Emilia, via Campi 183, 41125 Modena, Italy	Heinrich Sticht h.sticht@biochem.uni-erlangen.de Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstr. 17, 91054, Erlangen, Germany	Jie Zhang zhj8623@mail.xjtu.edu.cn Xi'an Jiaotong University, No. 76, Yanta West Road, Xi'an, Shaanxi Province 710061, PR China
David P. Fairlie d.fairlie@imb.uq.edu.au The University of Queensland, Brisbane, QLD 4072, Australia	G. Andrés Cisneros andres@chem.wayne.edu. Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202, United States	Hiram Ponce hiram.ponce@itesm.mx Universidad Panamericana, Mexico City, Mexico	Jie-Lou Liao liaojl@ustc.edu.cn. University of Science and Technology of China, 96 Jinzhai Road, 230026 Hefei, Anhui Province, People's Republic of China
Dhananjay Bhattacharyya dhananjay.bhattacharyya@saha.ac. in Saha Institute of Nuclear Physics, 1/AF Bidhannagar, Kolkata, 700064, India	Garikapati Narahari Sastry gnsastry@gmail.com CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad, India	Huaiyu Yang hyyang@simm.ac.cn. Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China	Jingdong Zhang jz@kemi.dtu.dk. Technical University of Denmark, 2800 Kongens Lyngby, Denmark
Dmytro M. Hovorun Taras Shevchenko National University of Kyiv, 2-h Akademika Hlushkova Ave., Kyiv 03022, Ukraine	Gerry A. F. Nicolaes g.nicolaes@maastrichtuniversity.nl . Maastricht University, 6200 MD Maastricht, The Netherlands	Hyun-Ju Park hyunju85@skku.edu Sungkyunkwan University, Suwon, 440-746, South Korea	José L. Medina-Franco medinajl@unam.mx Universidad Nacional Autónoma de México, Avenida Universidad 3000, Mexico City 04510, Mexico
Dongping Zhong zhong.28@osu.edu. The Ohio State University, Columbus, Ohio 43210, United States	Gilles Frison gilles.frison@polytechnique.edu Ecole Polytechnique and CNRS, Palaiseau Cedex, France	Ignacio Aliagas aliagas@gene.com Genentech Inc., 1 DNA Way, South San Francisco, CA, 94080, USA	Ju-Guang Han University of Science and Technology of China, Hefei 230029, P.R. China
E. Prabhu Raman prabhu@outerbanks.umaryland.edu University of Maryland School of Pharmacy, 20 Penn Street HSF II, Baltimore, Maryland 21201, United States	Guanghong Wei ghwei@fudan.edu.cn. Fudan University, 220 Handan Road, Shanghai 200433, China	Isabelle Krimm isabelle.krimm@univ-lyon1.fr. Université Lyon 1, F-69100 Villeurbanne, France	Ju-Guang Han University of Science and Technology of China, Hefei 230029, People's Republic of China
Eduardo Chamorro, echamorro@unab.cl Universidad Andres Bello,	Guanghong Wei ghwei@fudan.edu.cn. Fudan University,	J. Sponer sponer@ncbr.muni.cz.	

Juliana Palma liana@unq.edu.ar Universidad Nacional de Quilmes, Bernal, Argentina	Li-Qiang Feng, lqfeng_lngy@126.com Liaoning University of Technology, Jinzhou, 121000, China	Martin Gruebele University of Illinois, Urbana, Illinois 61801, United States	Mohammad Sadegh Sadeghi Googheri, sadeghi.mohammadsadegh@gmail. com Ferdowsi University of Mashhad, Mashhad, Iran
Julien Michel mail@julienmichel.net. Joseph Black Building, West Mains Road, Edinburgh EH9 3JJ, United Kingdom	Likai Du, dulk@qibebt.ac.cn (L. Du) Chinese Academy of Sciences, Qingdao, Shandong, People's Republic of China	Martin T. Stiebritz martin.stiebritz@phys.chem.ethz.c h Laboratorium für Physikalische Chemie, ETH Zürich, Zürich, Switzerland	Necmettin Pirinçcioglu pirincn@dicle.edu.tr University of Dicle, Diyarbakir, 21280, Turkey
Junshui Ma, junshui_ma@merck.com. Merck Research Laboratories, Rahway, New Jersey 07065, United States	M. Hosseinzadeh mhdshhosseinzadeh@gmail.com University of Guilan, P.O. Box 3756, Rasht, Iran	Masataka Nagaoka mnagaoka@is.nagoya-u.ac.jp; Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan	Noam Agmon agmon@fh.huji.ac.il. The Hebrew University of Jerusalem, Jerusalem 91904, Israel
Jyotirmayee Mohanty, jyotim@barc.gov.in. Bhabha Atomic Research Centre, Trombay, Mumbai 400085, India	M. Merz, Jr. kmerz1@gmail.com. Michigan State University, Room 283B, 578 South Shaw Lane, East Lansing, Michigan 48824, United States	Massimiliano Aschi massimiliano.aschi@univaq.it Universita' di l'Aquila, ' Aquila, Italy	Osman Canko, canko@erciyes.edu.tr Nevsehir Haci Bektas Veli University, Nevsehir, Turkey
Karunakar Kar karunakarkar@gmail.com Indian Institute of Technology Jodhpur, Old Residency Road, Jodhpur, 342011, Rajasthan, India	M. Teresa Pisabarro mayte.pisabarro@biotec.tu- dresden.de Biotech TU Dresden, Tatzberg 47-51, 01037, Dresden, Germany	Mehdi D. Esrafil, esrafil@maragheh.ac.ir University of Maragheh, Maragheh, Iran	P. B. Armentrout armentrout@chem.utah.edu. University of Utah, Salt Lake City, Utah 84112, United States
Khaled Barakat Kbarakat@ualberta.ca University of Alberta, Edmonton, AB, Canada	Maciej Przybyłek, m.przybylek@cm.umk.pl Nicolaus Copernicus University in Toruń, Kurpińskiego 5, 85-950, Bydgoszcz, Poland	Mehdi D. Esrafil, esrafil@maragheh.ac.ir University of Maragheh, Maragheh, Iran	Paul A. Keller keller@uow.edu.au University of Wollongong, 2522, Australia
Khaled H. Barakat, Kbarakat@ualberta.ca. University of Alberta, Edmonton, Alberta Canada	Madhumita Barooah m17barooah@yahoo.co.in Assam Agricultural University, Jorhat -785013, Assam, India	Michael Feig feig@msu.edu. Michigan State University, East Lansing, Michigan 48824, United States	Peng Zhou p_zhou@uestc.edu.cn. University of Electronic Science and Technology of China (UESTC), Chengdu 610054, China
Kim Bolton kim.bolton@hb.se University of Borås, SE 501-90, Borås, Sweden	Magdalena Pecul mpecul@chem.uw.edu.pl. University of Tromsø–The Arctic University of Norway, N-9037 Tromsø, Norway	Michal Otyepka, michal.otyepka@upol.cz. Palacký University, 17 Listopadu 12, 77146 Olomouc, Czech Republic	Peter Politzer, ppolitze@uno.ed University of New Orleans, New Orleans, LA, 71048, USA
Klaus R. Liedl Klaus.Liedl@uibk.ac.at. University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Tyrol, Austria	Maria Wallin maria.wallin@chalmers.se Chalmers University of Technology, 412 96, Göteborg, Sweden	Mihaly Mezei Icahn School of Medicine at Mount Sinai, New York, NY, USA	Phillip Choi phillip.choi@ualberta.ca University of Alberta, Edmonton, T6G 2V4, Canada
Lauren J. Webb lwebb@cm.utexas.edu. The University of Texas at Austin, Austin, Texas 78712, United States	Mark J. Stevens msteve@sandia.gov. Sandia National Laboratories, Albuquerque, New Mexico 87185- 1315, United States	Ming Lei leim@mail.buct.edu.cn Beijing University of Chemical Technology, Beijing 100029, PR China	Piotr Matczak, p.a.matczak@gmail.com University of Łódź, Pomorska 163/165, 90-236, Lodz, Poland
Leszek Zbigniew Ciunik leszek.ciunik@chem.uni.wroc.pl University of Wrocław, F. Joliot-Curie 14, 50-383, Wrocław, Poland			Ponnadurai Ramasami p.ramasami@uom.ac.mu University of Mauritius,

Réduit, 80837, Moka, Mauritius	Kalina, Santacruz [E], Mumbai 400098, India	Malaysia	Vanessa Ortiz vortiz@columbia.edu Columbia University, Dept. Chemical Engineering, United States
Prabha Garg National Institute of Pharmaceutical Education and Research (NIPER), Sector-67, S.A.S. Nagar 160 062, Punjab, India	Rajesh K. Murarka rkm@iiserb.ac.in. Indian Institute of Science Education and Research Bhopal, Indore By-pass Road, Bhauri, Bhopal 462066, MP, India	Shiang-Tai Lin stlin@ntu.edu.tw National Taiwan University, Taipei, Taiwan	Vishal Trivedi vtrivedi@iitg.ernet.in Indian Institute of Technology- Guwahati, Guwahati 781039, Assam, India
Pradeep Kumar Naik pknaik1973@gmail.com Jaypee University of Information Technology, Waknaghat, Distt. Solan, 173 234, Himachal Pradesh, India	Ramaswamy Amutha ramutha@bicpu.edu.in Pondicherry University, Puducherry, 605014, India	Staš Bevc stas.bevc@cmm.ki.si National Institute of Chemistry, Ljubljana, Slovenia	Wei Zhao wxzhao@ualr.edu. University of Arkansas at Little Rock, 2801 South University Avenue, Little Rock, Arkansas 72204, United States
Priyanka Sen priyankarjsr@gmail.com Utkal University, Bhubaneswar, India	Robert B. Best robertbe@helix.nih.gov National Institutes of Health, Bethesda, Maryland 20892, United States	Steven D. Schwartz sschwartz@email.arizona.edu. University of Arizona, 1306 East University Boulevard, Tucson, Arizona 85721, United States	Wenjie Fan, fanwenjie78@gmail.com Liaoning University of Technology, Jinzhou 121001, PR China
Qiang Shao qshao@mail.shcnc.ac.cn. Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China	Robert I. Cukier cukier@chemistry.msu.edu. Michigan State University, East Lansing, Michigan 48824- 1322, United States	Sudha Ramaiah VIT University, Vellore 632 014, Tamil Nadu, India	William G. Noid wnoid@chem.psu.edu. The Pennsylvania State University, University Park, Pennsylvania 16802, United States
R. Miller miller@mpikg.mpg.de. Sharif University of Technology, Teheran 11365-11155, Iran	Robert P. Sheridan sheridan@merck.com. Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, United States	Takahito Nakajima nakajima@riken.jp Advanced Institute for Computational Science, Chuo, Kobe, Hyogo, Japan	Wojciech Plazinski, wojtek_plazinski@o2.pl Polish Academy of Sciences, Niezapominajek Str., 8, 30-239, Cracow, Poland
Rabindra Roy rr228@georgetown.edu Georgetown University, Washington, DC 20057, United States	Ryan Taylor , ryanmt@byu.net Brigham Young University, Provo, UT 84602, USA	Thomas K. Haxton tomhaxton@gmail.com. Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States	Wonpil Im wonpil@ku.edu. The University of Kansas, 2030 Becker Drive, Lawrence, Kansas 66047, United States
Radhakrishnan Sarangapani, sradha78@yahoo.com High Energy Materials Research Laboratory, Pune 411 021, India	Sako Mirzaie, Islamic Azad University, Sanandaj, Iran	Tibor Dubaj, tibor.dubaj@stuba.sk Slovak University of Technology, Bratislava, Slovakia	Xiang Simon Wang x.simon.wang@gmail.com Howard University, 2300 Fourth Street NW, Washington, D.C. 20059, United States
Radomir Jasiński, radomir@chemia.pk.edu.pl Cracow University of Technology, Warszawska 24, 31-155, Cracow, Poland	Sandip Paul sandipp@iitg.ernet.in. Indian Institute of Technology, Guwahati 781039, Assam, India	Tomás Rocha-Rinza tomasrocharinza@gmail.com, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México, D. F., México	Xiang Zhao xzhaio@mail.xjtu.edu.cn Xi'an Jiaotong University, Xi'an, China
Rafael Brüscheweiler bruschweiler.1@osu.edu. The Ohio State University, Columbus, Ohio 43210, United States	Sarangan Ravichandran, ravichandrans@mail.nih.gov Frederick National Laboratory for Cancer Research (FNLCR), P.O. Box B, Frederick, MD 21702, USA	U. Deva Priyakumar deva@iiit.ac.in International Institute of Information Technology, Hyderabad, India	Xinyuan Shi, shixinyuan01@163.com Beijing University of Chinese Medicine, Beijing 100102, China
Raghuvir R.S. Pissurlenkar Molecular Simulations Group, Bombay College of Pharmacy,	Sepideh Parvizpour, se.parvizpour@gmail.com Universiti Teknologi Malaysia, Johor,		

Yi-hong Ding
yhdd@jlu.edu.cn
Jilin University,
Changchun,
People's Republic of China

Ying Zhou
yzhou@swpu.edu.cn
Southwest Petroleum University,
Chengdu, 610500,
China

Yingzhe Liu,
liuyz_204@163.com
Xi'an Modern Chemistry Research
Institute,
Xi'an, 710065,
People's Republic of China

Yishan Chen
chenyishan916@163.com
Qujing Normal University,
Qujing, 655011,
Yunnan, China

Yiying Tong
ytong@msu.edu
Department of Computer Science
and Engineering,
Michigan State University,
Michigan

Yong Zhang,
yong.zhang@stevens.edu.
University of Delaware,
Newark, Delaware 19716,
United States

Yoshihiro Yamanishi
yamanishi@bioreg.kyushu-u.ac.jp.
Kyushu University,
6-10-1, Hakozaki, Higashi-ku,
Fukuoka, Fukuoka 812-8581,
Japan

You Han,
yhan@tju.edu.cn
Tianjin University,
Tianjin, 300072,
China

Youjun Zhou
zhuoyoujun@smmu.edu.cn
Second Military Medical
University,
Shanghai 200433,
China

Zhonghan Hu
zhonghanhu@jlu.edu.cn
Jilin University,
Changchun,
People's Republic of China

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Editor:

R.Mutyala.
MMCC Results
RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.
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Assistant Editors:

Anston Feenstra, Vrije Univ., Amsterdam, Netherlands
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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

How does a hydrocarbon staple affect peptide hydrophobicity?

Adelene Y. L. Sim [Bioinformatics Institute (A*STAR)] and Chandra Verma

J. Comp. Chem., **36**, 773–784, 2015.

Water is essential for the proper folding of proteins and the assembly of protein–protein/ligand complexes. How water regulates complex formation depends on the chemical and topological details of the interface. The dynamics of water in the interdomain region between an E3 ubiquitin ligase (MDM2) and three different peptides derived from the tumor suppressor protein p53 are studied using molecular dynamics. The peptides show bimodal distributions of interdomain water densities across a range of distances.

Medicinal Chemistry and Drug Design

In silico identification of novel kinase inhibitors by targeting B-Raf^{V600E} from natural products database

Zi-jie Wang, Zhi-ning Wan, Xu-dong Chen, Chuan-fang Wu, Guo-long Gao, Rong Liu, Zheng Shi, Jin-ku Bao [Sichuan University, Chengdu]

J. Mol. Mod., **21**, 102, 2015.

The Ras/Raf/MEK/ERK (MAPK) signaling pathway has gained much attention from scientific community for therapeutic intervention in the past decades, specifically in oncology. Notably, a most prevalent B-Raf^{V600E} mutant in Raf kinase family exhibits elevated kinase activity and results in constitutive activation of the MAPK pathway, thus making it a promising drug target for cancer therapy. Herein, virtual screening is applied to identify its potential inhibitors. Following the 25 ns molecular dynamic (MD) simulations, ZINC38541768, ZINC38541767, and ZINC12496469 are identified as B-Raf^{V600E} potential inhibitors in a DFG-in conformation.



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8013 Los Sabalos Street
San Diego, CA 92126
Tel. (858) 663-0162
e-mail: mmccresults@gmail.com

Dr. R. Mutyala,
RR Labs Inc., 8013 Los Sabalos St.
San Diego, CA 92126

Editors Emeritus: Bruce Gelin, Ph.D.
David Busath, M.D.

Dr. Gelin was founder of MMCC Results and edited volumes 1-6.
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Assistant Editors:

Sowmya .N
Rational Labs, Hyderabad., India
Sambasivareddy M
RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

Pyrazolo[3,4-*d*]pyrimidines as novel inhibitors of O-acetyl-l-serine sulphydrylase of *Entamoebahistolytica*: an in silico study

UmeshYadava [D.D.U. Gorakhpur University], Bindesh Kumar Shukla, MihirRoychoudhury, Devesh Kumar

J. Mol.Mod., **21**, 96, 2015.

Amoebiasis, a worldwide explosive epidemic, caused by the gastrointestinal anaerobic protozoan parasite *Entamoebahistolytica*, infects the large intestine and, in advance stages, liver, kidney, brain and lung. Metronidazole (MNZ)—the first line medicament against amoebiasis—is potentially carcinogenic to humans and shows significant side-effects. Docking simulations using Glide-SP demonstrate good agreement with reported biological activities of molecules **1–9** and indicate that molecules **2** and **4** may act as potential high affinity inhibitors.

Pocketome of Human Kinases: Prioritizing the ATP Binding Sites of (Yet) Untapped Protein Kinases for Drug Discovery

Andrea Volkamer, SamehEid, Samo Turk, Sabrina Jaeger, Friedrich Rippmann, and Simone Fulle [BioMed X Innovation Center]

J.Chem. Infor. and Mod. **55**, 538–549, 2015.

Protein kinases are involved in a variety of diseases including cancer, inflammation, and autoimmune disorders. Although the development of new kinase inhibitors is a major focus in pharmaceutical research, a large number of kinases remained so far unexplored in drug discovery projects. The selection and assessment of targets is an essential but challenging area. Today, a few thousands of experimentally determined kinase structures are available, covering about half of the human kinome. This large structural source allows guiding the target selection via structure-based druggability prediction approaches such as DoGSiteScorer.

Computational Polypharmacology Analysis of the Heat Shock Protein 90 Interactome

Andrew Anighoro, Dagmar Stumpfe, Kathrin Heikamp, Kristin Beebe, Leonard M. Neckers, Jürgen Bajorath, and Giulio Rastelli [University of Modena and Reggio Emilia]

J.Chem. Infor. and Mod. **55**, 676–686, 2015.

The design of a single drug molecule that is able to simultaneously and specifically interact with multiple biological targets is gaining major consideration in drug discovery. However, the rational design of drugs with a desired polypharmacology profile is still a challenging task, especially when these targets are distantly related or unrelated. In this work, we present a computational approach aimed at the identification of suitable target combinations for multitarget drug design within an ensemble of biologically relevant proteins.

Pharmacophore modeling improves virtual screening for novel peroxisome proliferator-activated receptor-gamma ligands

Stephanie N. Lewis [Genetics, Bioinformatics, and Computational Biology Program, Virginia Tech], Zulma Garcia, Raquel Hontecillas, JosepBassaganya-Riera, David R. Bevan

J.Comp.Aided. Mol.des. **29**, 421-439, 2015.

Peroxisome proliferator-activated receptor-gamma (**PPAR γ**) is a nuclear hormone receptor involved in regulating various metabolic and immune processes. The **PPAR** family of receptors possesses a large binding cavity that imparts promiscuity of ligand binding not common to other nuclear receptors. This feature increases the challenge of using computational methods to identify **PPAR**ligands that will dock favorably into a structural model. Utilizing both ligand- and structure-based pharmacophore methods, we sought to improve agonist prediction by grouping ligands according to pharmacophore features, and pairing models derived from these features with receptor structures for docking.

Medicinal Chemistry and Drug Design (Cont'd)

Covalent docking of selected boron-based serine beta-lactamase inhibitors

Jacopo Colombo, Sgrignani, Beatrice Novati, Giorgio
Grazioso [Università degli Studi di Milano]

J. Comp. Aided. Mol. des. **29**, 441-450, 2015.

AmpC β -lactamase is a hydrolytic enzyme conferring resistance to β -lactam antibiotics in multiple Gram-negative bacteria. Therefore, identification of non- β -lactam compounds able to inhibit the enzyme is crucial for the development of novel antibacterial therapies. In general, AmpC inhibitors have to engage the highly solvent-exposed catalytic site of the enzyme. Therefore, understanding the implications of ligand-protein induced-fit and water-mediated interactions behind the inhibitor-enzyme recognition process is fundamental for undertaking structure-based drug design process. Here, we focus on boronic acids, a promising class of beta-lactamase covalent inhibitors.

Amyloid β -Protein Assembly: The Effect of Molecular Tweezers CLR01 and CLR03

Xueyun Zheng, Deyu Liu, Frank-Gerrit Klärner, Thomas Schrader, Gal Bitan, and Michael T. Bowers [University of California, Santa Barbara]

J. Phys. Chem. B., **119**, 4831–4841, 2015.

The early oligomerization of amyloid β -protein ($A\beta$) has been shown to be an important event in the pathology of Alzheimer's disease (AD). Designing small molecule inhibitors targeting $A\beta$ oligomerization is one attractive and promising strategy for AD treatment. Here we used ion mobility spectrometry coupled to mass spectrometry (IMS-MS) to study the different effects of the molecular tweezers CLR01 and CLR03 on $A\beta$ self-assembly. CLR01 was found to bind to $A\beta$ directly and disrupt its early oligomerization. Moreover, CLR01 remodeled the early oligomerization of $A\beta_{42}$ by compacting the structures of dimers and tetramers and as a consequence eliminated higher-order oligomers.

Microtubules dual chemo and thermo-responsive depolymerization

Z. Li and L. Alisaraie [Memorial University of Newfoundland]

Proteins: Stru. Fun. & Bioinf., **83**, 970–981, 2015.

The effects of chemotherapeutic agent vinblastine versus low temperature of 277 K were investigated on the structure of $\alpha\beta$ -tubulin heterodimer by means of molecular dynamics simulations. Individual experiments have shown that the vinblastine-bound heterodimer, and its apo structure under low temperature of 277 K, both undergo conformational changes toward destabilization of the dimer as compared to the apo tubulin at 300 K. Both factors exhibited weakening of the longitudinal interactions of tubulin heterodimer through displacing dimer interfacial segments, resulting in dominant electrostatic repulsion at the interface of the subunits.

Host-Guest Systems

Deciphering the Specific High-Affinity Binding of Cucurbit[7]uril to Amino Acids in Water

Jong Wha Lee, Hyun Hee L. Lee, Young Ho Ko, Kimoon Kim, and Hugh I. Kim [Pohang University of Science and Technology]

J. Phys. Chem. B., **119**, 4628–4636, 2015.

This work presents a systematic study on the host–guest interactions between the macrocyclic host molecule cucurbit[7]uril (CB[7]) and amino acids (AAs) including three basic AAs (Lys, Arg, and His) and three aromatic AAs (Phe, Tyr, and Trp) to elucidate the origin of the high selectivity of CB[7] toward AA residues in proteins. Complex formation between CB[7] and each AA was examined in solution (by isothermal titration calorimetry and NMR) as well as in the gas phase (by ion mobility mass spectrometry and collision-induced dissociation), and the results were further combined with computational investigations.

1.2. Biopolymers

Bioinformatics and Cheminformatics

DISOPRED3: precise disordered region predictions with annotated protein-binding activity

David T. Jones[University College London] and Domenico Cozzetto

Bioinformatics. **31**, 857-863, 2015.

A sizeable fraction of eukaryotic proteins contain intrinsically disordered regions (IDRs), which act in unfolded states or by undergoing transitions between structured and unstructured conformations. We describe DISOPRED3, which extends its predecessor with new modules to predict IDRs and protein-binding sites within them. Based on recent CASP evaluation results, DISOPRED3 can be regarded as state of the art in the identification of IDRs, and our self-assessment shows that it significantly improves over DISOPRED2 because its predictions are more specific across the whole board and more sensitive to IDRs longer than 20 amino acids.

GASS: identifying enzyme active sites with genetic algorithms

Sandro C. Izidoro [Universidade Federal de Itajubá], Raquel C. de Melo-Minardi, and Gisele L. Pappa

Bioinformatics. **31**, 864-870, 2015.

Currently, 25% of proteins annotated in Pfam have their function unknown. One way of predicting proteins function is by looking at their active site, which has two main parts: the catalytic site and the substrate binding site. This article presents a new heuristic method, named genetic active site search (GASS), which searches for given active site 3D templates in unknown proteins. GASS results were compared with those catalogued in the catalytic site atlas (CSA) in four different datasets and compared with two other methods: amino acid pattern search for substructures and motif and catalytic site identification.

Bioinformatics and Cheminformatics (Cont'd)

MetaPSICOV: combining coevolution methods for accurate prediction of contacts and long range hydrogen bonding in proteins

David T. Jones [University College London], Tanya Singh, Tomasz Kosciolk, and Stuart Tetchner

Bioinformatics. **31**, 999-1006, 2015.

Recent developments of statistical techniques to infer direct evolutionary couplings between residue pairs have rendered covariation-based contact prediction a viable means for accurate 3D modelling of proteins, with no information other than the sequence required. To extend the usefulness of contact prediction, we have designed a new meta-predictor (MetaPSICOV) which combines three distinct approaches for inferring covariation signals from multiple sequence alignments, considers a broad range of other sequence-derived features and, uniquely, a range of metrics whBioinformatics Group, University College London, describe both the local and global quality of the input multiple sequence alignment.

CRISPRdirect: software for designing CRISPR/Cas guide RNA with reduced off-target sites

Yuki Naito [Research Organization of Information and Systems, 1111 Yata], Kimihiro Hino, Hidemasa Bono, and Kumiko Ui-Tei

Bioinformatics. **31**, 1120-1123, 2015.

CRISPRdirect is a simple and functional web server for selecting rational CRISPR/Cas targets from an input sequence. The CRISPR/Cas system is a promising technique for genome engineering which allows target-specific cleavage of genomic DNA guided by Cas9 nuclease in complex with a guide RNA (gRNA), that complementarily binds to a ~20 nt targeted sequence. The target sequence requirements are twofold. First, the 5'-NGG protospacer adjacent motif (PAM) sequence must be located adjacent to the target sequence. Second, the target sequence should be specific within the entire genome in order to avoid off-target editing.

SAMNetWeb: identifying condition-specific networks linking signaling and transcription

Coyin Oh, and Ernest Fraenkel [Massachusetts Institute of Technology, Cambridge]

Bioinformatics. **31**, 1124-1126, 2015.

High-throughput datasets such as genetic screens, mRNA expression assays and global phospho-proteomic experiments are often difficult to interpret due to inherent noise in each experimental system. Computational tools have improved interpretation of these datasets by enabling the identification of biological processes and pathways that are most likely to explain the measured results. We introduce SAMNetWeb, a web-based tool that enables functional enrichment analysis and visualization of high-throughput datasets. SAMNetWeb can analyse two distinct data types simultaneously across multiple experimental systems to identify pathways activated in these experiments.

GenomeCons: a web server for manipulating multiple genome sequence alignments and their consensus sequences

Tetsuya Sato[CREST, Japan Science and Technology Agency] and MikitaSuyama

Bioinformatics. **31**, 1293-1295, 2015.

Genome sequence alignments provide valuable information on many aspects of molecular biological processes. In this study, we developed a web server, GenomeCons, for manipulating multiple genome sequence alignments and their consensus sequences for high-throughput genome sequence analyses. This server facilitates the visual inspection of multiple genome sequence alignments for a set of genomic intervals at a time. This allows the user to examine how these sites are evolutionarily conserved over time for their functional importance.

Bioinformatics and Cheminformatics (Cont'd)

New Publicly Available Chemical Query Language, CSRML, To Support Chemotype Representations for Application to Data Mining and Modeling

Chihae Yang [Molecular Networks GmbH], Aleksey Tarkhov, Jörg Maruszyk, Bruno Bienfait, Johann Gasteiger, Thomas Kleinoeder, Tomasz Magdziarz, Oliver Sacher, Christof H. Schwab, Johannes Schwoebel, Lothar Terfloth, Kirk Arvidson, Ann Richard, Andrew Worth, and James Rathman

J.Chem. Infor. and Mod. **55**, 510–528, 2015.

Chemotypes are a new approach for representing molecules, chemical substructures and patterns, reaction rules, and reactions. Chemotypes are expressed in the XML-based Chemical Subgraphs and Reactions Markup Language (CSRML), and can be encoded not only with connectivity and topology but also with properties of atoms, bonds, electronic systems, or molecules. CSRML has been developed in parallel with a public set of chemotypes, i.e., the ToxPrintchemotypes, which are designed to provide excellent coverage of environmental, regulatory, and commercial-use chemical space, as well as to represent chemical patterns and properties especially relevant to various toxicity concerns.

Metabolic Pathway Predictions for Metabolomics: A Molecular Structure Matching Approach

Mai A. Hamdalla, Sanguthevar Rajasekaran, David F. Grant, and Ion I. Măndoiu [University of Connecticut, Storrs]

J.Chem. Infor. and Mod. **55**, 709–718, 2015.

Metabolic pathways are composed of a series of chemical reactions occurring within a cell. In each pathway, enzymes catalyze the conversion of substrates into structurally similar products. Thus, structural similarity provides a potential means for mapping newly identified biochemical compounds to known metabolic pathways. In this paper, we present TrackSM, a cheminformatics tool designed to associate a chemical compound to a known metabolic pathway based on molecular structure matching techniques. Validation experiments show that TrackSM is capable of associating 93% of tested structures to their correct KEGG pathway class and 88% to their correct individual KEGG pathway.

An On-the-Fly Surface-Hopping Program JADE for Nonadiabatic Molecular Dynamics of Polyatomic Systems: Implementation and Applications

Likai Du and Zhenggang Lan [Chinese Academy of Sciences, Qingdao]

J. Chem. Theor. and Comp. **11**, 1360–1374, 2015.

Nonadiabatic dynamics simulations have rapidly become an indispensable tool for understanding ultrafast photochemical processes in complex systems. Here, we present our recently developed on-the-fly nonadiabatic dynamics package, JADE, which allows researchers to perform nonadiabatic excited-state dynamics simulations of polyatomic systems at an all-atomic level. The nonadiabatic dynamics is based on Tully's surface-hopping approach. Currently, several electronic structure methods (CIS, TDHF, TDDFT(RPA/TDA), and ADC(2)) are supported, especially TDDFT, aiming at performing nonadiabatic dynamics on medium- to large-sized molecules.

Protein Secondary Structure

In silico platform for predicting and initiating β -turns in a protein at desired locations

Harinder Singh, Sandeep Singh and Gajendra P. S. Raghava
[G. P. S. Raghava, Scientist & Head Bioinformatics Centre]

Proteins: Stru. Fun. & Bioinf., **83**, 910–921, 2015.

Numerous studies have been performed for analysis and prediction of β -turns in a protein. This study focuses on analyzing, predicting, and designing of β -turns to understand the preference of amino acids in β -turn formation. We analyzed around 20,000 PDB chains to understand the preference of residues or pair of residues at different positions in β -turns. Based on the results, a propensity-based method has been developed for predicting β -turns with an accuracy of 82%.

Protein Structure Prediction

Structure and dynamics of DRD4 bound to an agonist and an antagonist using in silico approaches

NidhiJatana, LipiThukral and N. Latha [Sri Venkateswara College (University of Delhi)]

Proteins: Stru. Fun. & Bioinf., **83**, 867–880, 2015.

Human dopamine receptor D4 (DRD4), a member of G-protein coupled receptor (GPCR) family, plays a central role in cell signaling and trafficking. Dysfunctional activity of DRD4 can lead to several psychiatric conditions and, therefore, represents target for many neurological disorders. However, lack of atomic structure impairs our understanding of the mechanism regulating its activity. Here, we report the modeled structure of DRD4 alone and in complex with dopamine and spiperone, its natural agonist and antagonist, respectively.

Optimized distance-dependent atom-pair-based potential DOOP for protein structure prediction

Myong-Ho Chae, Florian Krull and Ernst-Walter Knapp
[University of Science, Pyongyang]

Proteins: Stru. Fun. & Bioinf., **83**, 881–890, 2015.

The DOcking decoy-based Optimized Potential (DOOP) energy function for protein structure prediction is based on empirical distance-dependent atom-pair interactions. To optimize the atom-pair interactions, native protein structures are decomposed into polypeptide chain segments that correspond to structural motives involving complete secondary structure elements. They constitute near native ligand–receptor systems (or just pairs). Thus, a total of 8609 ligand–receptor systems were prepared from 954 selected proteins.

Comparative or Homology Modeling

Structural Insight into Tetrameric hTRPV1 from Homology Modeling, Molecular Docking, Molecular Dynamics Simulation, Virtual Screening, and Bioassay Validations

Zhiwei Feng, Larry V. Pearce, Xiaomeng Xu, Xiaole Yang, Peng Yang, Peter M. Blumberg, and Xiang-QunXie [University of Pittsburgh]

J.Chem. Infor. and Mod. **55**, 572–588, 2015.

The transient receptor potential vanilloid type 1 (TRPV1) is a heat-activated cation channel protein, which contributes to inflammation, acute and persistent pain. Antagonists of human TRPV1 (hTRPV1) represent a novel therapeutic approach for the treatment of pain. Developing various antagonists of hTRPV1, however, has been hindered by the unavailability of a 3D structure of hTRPV1. Recently, the 3D structures of rat TRPV1 (rTRPV1) in the presence and absence of ligand have been reported as determined by cryo-EM. rTRPV1 shares 85.7% sequence identity with hTRPV1. In the present work, we constructed and reported the 3D homology tetramer model of hTRPV1 based on the cryo-EM structures of rTRPV1.

Protein Confirmational Analysis

Enhanced conformational sampling method for proteins based on the TaBooSeArch algorithm: Application to the folding of a mini-protein, chignolin

Ryuhei Harada, Yu Takano and Yasuteru Shigeta [University of Tsukuba]

J. Comp. Chem., **36**, 763–772, 2015.

The conformational samplings are indispensable for obtaining reliable canonical ensembles, which provide statistical averages of physical quantities such as free energies. However, the samplings of vast conformational space of biomacromolecules by conventional molecular dynamics (MD) simulations might be insufficient, due to their inadequate accessible time-scales for investigating biological functions. Therefore, the development of methodologies for enhancing the conformational sampling of biomacromolecules still remains as a challenging issue in computational biology.

Molecular dynamics simulation and conformational analysis of some catalytically active peptides

Bahareh Honarparvar [University of KwaZulu-Natal], Adam A. Skelton

J. Mol.Mod., **21**, 100, 2015.

The design of stable and inexpensive artificial enzymes with potent catalytic activity is a growing field in peptide science. The first step in this design process is to understand the key factors that can affect the conformational preference of an enzyme and correlate them with its catalytic activity. In this work, molecular dynamics simulations in explicit water of two catalytically active peptides (peptide 1: Fmoc-Phe₁-Phe₂-His-CONH₂; peptide 2: Fmoc-Phe₁-Phe₂-Arg-CONH₂) were performed at temperatures of 300, 400, and 500 K

Protein Conformational Analysis (Cont'd)

Identification of Mutational Hot Spots for Substrate Diffusion: Application to Myoglobin

David De Sancho, Adam Kubas, Po-Hung Wang, JochenBlumberger, and Robert B. Best [National Institute of Diabetes and Digestive and Kidney Diseases,National Institutes of Health, Bethesda]

J. Chem. Theor. and Comp, **11**, 1919–1927, 2015.

The pathways by which small molecules (substrates or inhibitors) access active sites are a key aspect of the function of enzymes and other proteins. A key problem in designing or altering such proteins is to identify sites for mutation that will have the desired effect on the substrate transport properties. While specific access channels have been invoked in the past, molecular simulations suggest that multiple routes are possible, complicating the analysis. This complexity, however, can be captured by a Markov State Model (MSM) of the ligand diffusion process. We have developed a sensitivity analysis of the resulting rate matrix, which identifies the locations where mutations should have the largest effect on the diffusive on rate.

Evaluation of conformational changes in diabetes-associated mutation in insulin a chain: A molecular dynamics study

Yong Hwan Kim, Kevin Kastner, Badi Abdul-Wahid and Jesús A. Izaguirre [University of Notre Dame]

Proteins: Stru. Fun. & Bioinf., **83**, 662–669, 2015.

Insulin plays a central role in the regulation of metabolism in humans. Mutations in the insulin gene can impair the folding of its precursor protein, proinsulin, and cause permanent neonatal-onset diabetes mellitus known as Mutant INS-gene induced Diabetes of Youth (MIDY) with insulin deficiency. To gain insights into the molecular basis of this diabetes-associated mutation, we perform molecular dynamics simulations in wild-type and mutant (Cys^{A7} to Tyr or C(A7)Y) insulin A chain in aqueous solutions. The C(A7)Y mutation is one of the identified mutations that impairs the protein folding by substituting the cysteine residue which is required for the disulfide bond formation.

Key mutations stabilize antigen-binding conformation during affinity maturation of a broadly neutralizing influenza antibody lineage

Huafeng Xu, Aaron G. Schmidt, Timothy O'Donnell, Matthew D. Therkelsen, Thomas B. Kepler, M. Anthony Moody, Barton F. Haynes, Hua-Xin Liao, Stephen C. Harrison and David E. Shaw [D. E. Shaw Research, New York]

Proteins: Stru. Fun. & Bioinf., **83**, 771–780, 2015.

Affinity maturation, the process in which somatic hypermutation and positive selection generate antibodies with increasing affinity for an antigen, is pivotal in acquired humoral immunity. Previous work showed that increased affinity in the mature antibodies derives primarily from stabilization of the CDR H3 loop in the antigen-binding conformation. We have now used molecular dynamics simulations and existing crystal structures to identify potentially key maturation mutations, and we have characterized their effects on the CDR H3 loop and on antigen binding using further simulations and experimental affinity measurements, respectively.

Protein Conformational Analysis (Cont'd)

Conformational and connotational heterogeneity: A surprising relationship between protein structural flexibility and puns

Daniel A. Keedy [University of California, San Francisco]

Proteins: Stru. Fun. & Bioinf., **83**, 797–798, 2015.

Protein structures are often thought of as static objects, and indeed, the bulk of a protein's sequence forms α -helices, β -sheets, and other generally well-ordered substructures. These portions of the molecule pre-pay the entropic price of maintaining a globally unique fold, freeing other regions to adopt multiple alternative conformations. In many cases, this localized flexibility is biologically interesting: it may be important for catalytic turnover or for conformational selection before forming an intermolecular complex, for example. This linguistic scaffolding in some sense pre-pays a rhetorical price, paving the way for punctuated instances in which a given word or phrase can simultaneously adopt multiple alternative connotations—in other words, for puns.

Determining and visualizing flexibility in protein structures

Walter R. P. Scott and Suzana K. Straus [University of British Columbia]

Proteins: Stru. Fun. & Bioinf., **83**, 820–826, 2015.

How to compare the structures of an ensemble of protein conformations is a fundamental problem in structural biology. As has been previously observed, the widely used RMSD measure due to Kabsch, in which a rigid-body superposition minimizing the least-squares positional deviations is performed, has its drawbacks when comparing and visualizing a set of flexible protein structures. Here, we develop a method, fleximatch, of protein structure comparison that takes flexibility into account.

Protein Structure Analysis

Significant Refinement of Protein Structure Models Using a Residue-Specific Force Field

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

J. Chem. Theor. and Comp., **11**, 1949–1956, 2015.

An important application of all-atom explicit-solvent molecular dynamics (MD) simulations is the refinement of protein structures from low-resolution experiments or template-based modeling. A critical requirement is that the native structure is stable with the force field. We have applied a recently developed residue-specific force field, RSFF1, to a set of 30 refinement targets from recent CASP experiments. Starting from their experimental structures, 1.0 μ s unrestrained simulations at 298 K retain most of the native structures quite well except for a few flexible terminals and long internal loops.

X-ray crystallographic validation of structure predictions used in computational design for protein stabilization

Robert J. Floor, Hein J. Wijma, Peter A. Jekel, Anke C. Terwisscha van Scheltinga, Bauke W. Dijkstra and Dick B. Janssen [University of Groningen, Groningen]

Proteins: Stru. Fun. & Bioinf., **83**, 940–951, 2015.

Protein engineering aimed at enhancing enzyme stability is increasingly supported by computational methods for calculation of mutant folding energies and for the design of disulfide bonds. To examine the accuracy of mutant structure predictions underlying these computational methods, crystal structures of thermostable limonene epoxide hydrolase variants obtained by computational library design were determined.

Protein Dynamics

HYCUD: a computational tool for prediction of effective rotational correlation time in flexible proteins

NasrollahRezaei-Ghaleh, Frederik Klama, Francesca Munari, and Markus Zweckstetter [Max Planck Institute for Biophysical Chemistry]

Bioinformatics. **31**, 1319-1321, 2015.

A large fraction of eukaryotic proteins contain unstructured tails or linkers. The presence of flexible regions allows these systems to experience a high level of mobility facilitating their biological function. The complex nature of protein rotation in such flexible modular systems precludes a straightforward application of hydrodynamic methods to calculate their rotational motional properties. We describe the workflow of HYdrodynamicCoUpling of Domains (HYCUD), a program for prediction of effective rotational correlation times in multidomain proteins.

Mechanisms of the self-assembly of EAK16-family peptides into fibrillar and globular structures: molecular dynamics simulations from nano- to micro-seconds

SoheilaEmamyari, FaezehKargar, Vahid Sheikh-hasani, Saeed Emadi, Hossein Fazli [Institute for Advanced Studies in Basic Sciences (IASBS)]

Eur.Biophy., **44**, 263-276, 2015.

The self-assembly of EAK16-family peptides in a bulk solution was studied using a combination of all-atom and coarse-grained molecular dynamics simulations. In addition, specified concentrations of EAK16 peptides were induced to form fibrillary or globular assemblies in vitro. The results show that the combination of all-atom molecular dynamics simulations on the single- and double-chain levels and coarse-grained simulations on the many-chain level predicts the experimental observations reasonably well.

A dimension map for molecular aggregates

Cuiying Jian, Tian Tang [Water Planet Engineering, 721D, South Glasgow Avenue], SubirBhattacharjee

J. Mol.Graph. and Mod., **58**, 10-15,2015.

A pair of gyradius ratios, defined from the principal radii of gyration, are used to generate a dimension map that describes the geometry of molecular aggregates in water and in organic solvents. Molecular dynamics simulations were performed on the aggregation of representative biomolecules and polyaromatic compounds to demonstrate application of the dimension map. It was shown that molecular aggregate data on the dimension map were bounded by two boundary curves, and that the map could be separated into three regions representing three groups of structures: one-dimensional rod-like structures; two-dimensional planar structures or short-cylinder-like structures; and three-dimensional sphere-like structures.

New Insights into the Molecular Mechanism of E-Cadherin-Mediated Cell Adhesion by Free Energy Calculations

Fabio Doro, Giorgio Saladino, Laura Belvisi, Monica Civera, and Francesco L. Gervasio [University College London]

J. Chem. Theor. and Comp, **11**, 1354–1359, 2015.

Three-dimensional domain swapping is an important mode of protein association leading to the formation of stable dimers. Monomers associating via this mechanism mutually exchange a domain to form a homodimer. Classical cadherins, an increasingly important target for anticancer therapy, use domain swapping to mediate cell adhesion. However, despite its importance, the molecular mechanism of domain swapping is still debated. Here, we study the conformational changes that lead to activation and dimerization via domain swapping of E-cadherin. Using state-of-the-art enhanced sampling atomistic simulations, we reconstruct its conformational free energy landscape, obtaining the free energy profile connecting the inactive and active form.

Protein Dynamics (Cont'd)

Protein Simulations in Fluids: Coupling the OPEP Coarse-Grained Force Field with Hydrodynamics

Fabio Sterpone [Univ. Paris Diderot], Philippe Derreumaux, and Simone Melchionna

J. Chem. Theor. and Comp., **11**, 1843–1853, 2015.

A novel simulation framework that integrates the OPEP coarse-grained (CG) model for proteins with the Lattice Boltzmann (LB) methodology to account for the fluid solvent at mesoscale level is presented. OPEP is a very efficient, water-free and electrostatic-free force field that reproduces at quasi-atomistic detail processes like peptide folding, structural rearrangements, and aggregation dynamics. The LB method is based on the kinetic description of the solvent in order to solve the fluid mechanics under a wide range of conditions, with the further advantage of being highly scalable on parallel architectures.

Picosecond Fluorescence Dynamics of Tryptophan and 5-Fluorotryptophan in Monellin: Slow Water-Protein Relaxation Unmasked

Jianhua Xu, Binbin Chen, Patrik Callis, Pedro L. Muiño, Henriëtte Rozeboom, Jaap Broos, Dmitri Toptygin, Ludwig Brand, and Jay R. Knutson [National Institutes of Health, Bethesda]

J. Phys. Chem. B., **119**, 4230–4239, 2015.

Time dependent fluorescence Stokes (emission wavelength) shifts (TDFSS) from tryptophan (Trp) following sub-picosecond excitation are increasingly used to investigate protein dynamics, most recently enabling active research interest into water dynamics near the surface of proteins. Unlike many fluorescence probes, both the efficiency and the wavelength of Trp fluorescence in proteins are highly sensitive to microenvironment, and Stokes shifts can be dominated by the well-known heterogeneous nature of protein structure, leading to what we call pseudo-TDFSS: shifts that arise from differential decay rates of subpopulations.

The Role of Multifilament Structures and Lateral Interactions in Dynamics of Cytoskeleton Proteins and Assemblies

Xin Li and Anatoly B. Kolomeisky [Rice University]

J. Phys. Chem. B., **119**, 4653–4661, 2015.

Microtubules and actin filaments are biopolymer molecules that are major components of cytoskeleton networks in biological cells. They play important roles in supporting fundamental cellular processes such as cell division, signaling, locomotion, and intracellular transport. In cells, cytoskeleton proteins function under nonequilibrium conditions that are powered by hydrolysis of adenosine triphosphate (ATP) or guanosine triphosphate (GTP) molecules attached to them. Although these biopolymers are critically important for all cellular processes, the mechanisms that govern their complex dynamics and force generation remain not well explained.

Solubility of Cellulose in Supercritical Water Studied by Molecular Dynamics Simulations

Lasse K. Tolonen, Malin Bergenstråhle-Wohlert, Herbert Sixta, and Jakob Wohlert [Aalto University]

J. Phys. Chem. B., **119**, 4739–4748, 2015.

The insolubility of cellulose in ambient water and most aqueous systems presents a major scientific and practical challenge. Intriguingly though, the dissolution of cellulose has been reported to occur in supercritical water. In this study, cellulose solubility in ambient and supercritical water of varying density (0.2, 0.7, and 1.0 g cm⁻³) was studied by atomistic molecular dynamics simulations using the CHARMM36 force field and TIP3P water. The Gibbs energy of dissolution was determined between a nanocrystal (4 × 4 × 20 anhydroglucose residues) and a fully dissociated state using the two-phase thermodynamics model.

Protein Dynamics (Cont'd)

Conformational Dependence of the Circular Dichroism Spectra of Single Amino Acids from Plane-Waves-Based Density Functional Theory Calculations

E. Molteni, G. Onida, and G. Tiana [Università degli Studi di Milano]

J. Phys. Chem. B., **119**, 4803–4811, 2015.

We study the conformational dependence of circular dichroism (CD) spectra of amino acid molecules by means of an efficient *ab initio* DFT approach which is free from the typical gauge invariance issues arising with the use of localized basis sets and/or real-space grids. We analyze the dependence of the chiroptical spectra on the backbone dihedrals in the specific case of alanine and consider the role of side chain degrees of freedom at the examples of leucine, phenylalanine, and serine, whose side chains have different physicochemical properties.

Structural Dynamics and Thermostabilization of Neurotensin Receptor 1

Sangbae Lee, Supriyo Bhattacharya, Christopher G. Tate, Reinhard Grisshammer, and Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Phys. Chem. B., **119**, 4917–4928, 2015.

The neurotensin receptor NTSR1 binds the peptide agonist neurotensin (NTS) and signals preferentially via the G_q protein. Recently, Grisshammer and co-workers reported the crystal structure of a thermostable mutant NTSR1-GW5 with NTS bound. Understanding how the mutations thermostabilize the structure would allow efficient design of thermostable mutant GPCRs for protein purification, and subsequent biophysical studies. Using microsecond scale molecular dynamics simulations (4 μ s) of the thermostable mutant NTSR1-GW5 and wild type NTSR1, we have elucidated the structural and energetic factors that affect the thermostability and dynamics of NTSR1.

Prediction of VH–VL domain orientation for antibody variable domain modeling

Alexander Bujotzek [Roche Innovation Center Penzberg, Penzberg], James Dunbar, Florian Lipsmeier, Wolfgang Schäfer, Iris Antes, Charlotte M. Deane and Guy Georges

Proteins: Stru. Fun. & Bioinf., **83**, 681–695, 2015.

The antigen-binding site of antibodies forms at the interface of their two variable domains, VH and VL, making VH–VL domain orientation a factor that codetermines antibody specificity and affinity. Preserving VH–VL domain orientation in the process of antibody engineering is important in order to retain the original antibody properties, and predicting the correct VH–VL orientation has also been recognized as an important factor in antibody homology modeling. In this article, we present a fast sequence-based predictor that predicts VH–VL domain orientation with Q² values ranging from 0.54 to 0.73 on the evaluation set.

Nucleotide-dependent structural fluctuations and regulation of microtubule-binding affinity of KIF1A

Ryo Kanada, Fumiko Takagi and Macoto Kikuchi [Osaka University, Toyonaka]

Proteins: Stru. Fun. & Bioinf., **83**, 809–819, 2015.

Molecular motors such as kinesin regulate affinity to a rail protein during the ATP hydrolysis cycle. The regulation mechanism, however, is yet to be determined. To understand this mechanism, we investigated the structural fluctuations of the motor head of the single-headed kinesin called KIF1A in different nucleotide states using molecular dynamics simulations of a G δ -like model. We found that the helix $\alpha 4$ at the microtubule (MT) binding site intermittently exhibits a large structural fluctuation when MT is absent.

Protein Dynamics (Cont'd)

Genome-wide computational determination of the human metalloproteome

Ariel Azia, Ronen Levy, Ron Unger, Marvin Edelman and Vladimir Sobolev [Weizmann Institute of Science, Rehovot]

Proteins: Stru. Fun. & Bioinf., **83**, 931–939, 2015.

Accurate prediction of protein function in humans is important for understanding biological processes at the molecular level in biomedicine and drug design. Over a third of proteins are commonly held to bind metal, and ~10% of human proteins, to bind zinc. Therefore, an initial step in protein function prediction frequently involves predicting metal ion binding. In recent years, methods have been developed to predict a set of residues in 3D space forming the metal-ion binding site, often with a high degree of accuracy.

Free Energy Calculations

Guidelines for the analysis of free energy calculations

Pavel V. Klimovich, Michael R. Shirts, David L. Mobley [University of California, Irvine]

J.Comp.Aided. Mol.des. **29**, 397-411, 2015.

Free energy calculations based on molecular dynamics simulations show considerable promise for applications ranging from drug discovery to prediction of physical properties and structure-function studies. But these calculations are still difficult and tedious to analyze, and best practices for analysis are not well defined or propagated. Essentially, each group analyzing these calculations needs to decide how to conduct the analysis and, usually, develop its own analysis tools. Here, we review and recommend best practices for analysis yielding reliable free energies from molecular simulations.

Ligand Binding/Docking

Molecular Docking Screening Using Agonist-Bound GPCR Structures: Probing the A_{2A} Adenosine Receptor

David Rodríguez, Zhang-GuoGao, Steven M. Moss, Kenneth A. Jacobson, and Jens Carlsson [Stockholm University, Box 1031]

J.Chem. Infor. and Mod. **55**, 550–563, 2015.

Crystal structures of G protein-coupled receptors (GPCRs) have recently revealed the molecular basis of ligand binding and activation, which has provided exciting opportunities for structure-based drug design. The A_{2A} adenosine receptor (A_{2A}AR) is a promising therapeutic target for cardiovascular diseases, but progress in this area is limited by the lack of novel agonist scaffolds. We carried out docking screens of 6.7 million commercially available molecules against active-like conformations of the A_{2A}AR to investigate whether these structures could guide the discovery of agonists. Nine out of the 20 predicted agonists were confirmed to be A_{2A}AR ligands, but none of these activated the ARs.

Ligand Binding / Docking (Cont'd)

Predicted Structures for Kappa Opioid G-Protein Coupled Receptor Bound to Selective Agonists

Quanjie Li, Soo-Kyung Kim, William A. Goddard III [California Institute of Technology], Guangju Chen, and Hongwei Tan

J.Chem. Infor. and Mod. **55**, 614–627, 2015.

Human kappa opioid receptor (κ -OR), a G protein-coupled receptor (GPCR), has been identified as a drug target for treatment of such human disorders as pain perception, neuroendocrine physiology, affective behavior, and cognition. Indeed, there is an X-ray structure for an antagonist bound to κ -OR, but structures for activated GPCRs are quite different from those for the inactive GPCRs. We predict the ensemble of 24 low-energy structures of human kappa opioid receptor, obtained by application of the GEnSeMBLE complete sampling method, Evaluating 13 trillion combinations of tilt and rotation angles for κ -OR to select the best 24.

Tau Assembly: The Dominant Role of PHF6 (VQIVYK) in Microtubule Binding Region Repeat R3

Pritam Ganguly, Thanh D. Do, Luca Larini, Nichole E. LaPointe, Alexander J. Sercel, Madeleine F. Shade, Stuart C. Feinstein, Michael T. Bowers, and Joan-Emma Shea [University of California at Santa Barbara]

J. Phys. Chem. B., **119**, 4582–4593, 2015.

Self-aggregation of the microtubule-binding protein Tau reduces its functionality and is tightly associated with Tau-related diseases, termed tauopathies. Tau aggregation is also strongly associated with two nucleating six-residue segments, namely PHF6 (VQIVYK) and PHF6* (VQIINK). In this paper, using experiments and computational modeling, we study the self-assembly of individual and binary mixtures of Tau fragments containing PHF6* (R2/wt;²⁷³GKVQIINKKLDL²⁸⁴) and PHF6 (R3/wt;³⁰⁶VQIVYKPVDLSK³¹⁷) and a mutant R2/ Δ K280 associated with a neurodegenerative tauopathy.

Flexibility in the N-terminal actin-binding domain: Clues from in silico mutations and molecular dynamics

DevlinaChakravarty, SoumyanandaChakraborti and PinakChakrabarti [Department of Biochemistry, Bose Institute]

Proteins: Stru. Fun. & Bioinf., **83**, 696–710, 2015.

Dystrophin is a long, rod-shaped cytoskeleton protein implicated in muscular dystrophy (MDys). Utrophin is the closest autosomal homolog of dystrophin. Both proteins have N-terminal actin-binding domain (N-ABD), a central rod domain and C-terminal region. N-ABD, composed of two calponin homology (CH) subdomains joined by a helical linker, harbors a few disease causing missense mutations. In this investigation, we have used extensive molecular dynamics simulations to understand the differences and the similarities of these two proteins, along with another actin-binding protein, fimbrin.

Molecular modeling reveals binding interface of γ -tubulin with GCP4 and interactions with noscapinoids

Charu Suri, Harish C. Joshi and Pradeep Kumar Naik [Jaypee University of Information Technology]

Proteins: Stru. Fun. & Bioinf., **83**, 827–843, 2015.

The initiation of microtubule assembly within cells is guided by a cone shaped multi-protein complex, γ -tubulin ring complex (γ TuRC) containing γ -tubulin and atleast five other γ -tubulin-complex proteins (GCPs), i.e., GCP2, GCP3, GCP4, GCP5, and GCP6. The rim of γ TuRC is a ring of γ -tubulin molecules that interacts, via one of its longitudinal interfaces, with GCP2, GCP3, or GCP4 and, via other interface, with α/β -tubulin dimers recruited for the microtubule lattice formation. These interactions however, are not well understood in the absence of crystal structure of functional reconstitution of γ TuRC subunits. We elucidate the atomic interactions between γ -tubulin and GCP4 through computational techniques.

Ligand Binding / Docking (Cont'd)

Binding hotspots on K-ras: Consensus ligand binding sites and other reactive regions from probe-based molecular dynamics analysis

Priyanka Prakash, John F. Hancock and Alemayehu A. Gorfe
[University of Texas Health Science Center at Houston]

Proteins: Stru. Fun. & Bioinf., **83**, 898–909, 2015.

We have used probe-based molecular dynamics (pMD) simulations to search for interaction hotspots on the surface of the therapeutically highly relevant oncogenic K-Ras G12D. Combining the probe-based query with an ensemble-based pocket identification scheme and an analysis of existing Ras-ligand complexes, we show that (i) pMD is a robust and cost-effective strategy for binding site identification, (ii) all four of the previously reported ligand binding sites are suitable for structure-based ligand design, and (iii) in some cases probe binding and expanded sampling of configurational space enable pocket expansion and increase the likelihood of site identification.

Enzyme Catalysis

XenoSiteserver: a web-available site of metabolism prediction tool

Matthew K. Matlock, Tyler B. Hughes, and S. Joshua Swamidass [Washington University School of Medicine]

Bioinformatics. **31**, 1136-1137, 2015.

Cytochrome P450 enzymes (P450s) are metabolic enzymes that process the majority of FDA-approved, small-molecule drugs. Understanding how these enzymes modify molecule structure is key to the development of safe, effective drugs. XenoSite server is an online implementation of the XenoSite, a recently published computational model for P450 metabolism. XenoSite predicts which atomic sites of a molecule—sites of metabolism (SOMs)—are modified by P450s. XenoSite server accepts input in common chemical file formats including SDF and SMILES and provides tools for visualizing the likelihood that each atomic site is a site of metabolism for a variety of important P450s, as well as a flat file download of SOM predictions.

Molecular dynamics of the asymmetric dimers of EGFR: Simulations on the active and inactive conformations of the kinase domain

NapatSongtawee, David R. Bevan,
KiattaweeChoowongkamon [Faculty of Science,
Kasetsart University]

J. Mol.Graph. and Mod., **58**, 16-29,2015.

Abnormal activation of EGFR is associated with human cancer, and thus it is a key target for inhibition in cancer therapy. There is evidence suggesting that the activation mechanism of EGFR is based upon the formation of the asymmetric dimer of the kinase domains. Here, we performed MD simulations on the asymmetric dimer for both active and inactive conformations of EGFR kinase domain to investigate flexibility and intrinsic motions of the proteins. Simulations of the active conformation showed that the formation of the asymmetric dimer changes the dynamics of EGFR kinase domain by suppressing fluctuation of the protein and altering the direction of motion of the protein.

Enzyme Catalysis (Cont'd)

Molecular docking and molecular dynamics simulation of Trypanosomacruzi triosephosphate isomerase inhibitors. Insights into the inhibition mechanism and selectivity

Lucía Minini, Guzmán Álvarez, Mercedes González, Hugo Cerecetto, Alicia Merlino [Universidad de la República]

J. Mol. Graph. and Mod., **58**, 40-49, 2015.

Trypanosomacruzi (*T. cruzi*) triosephosphate isomerase (TcTIM) is a glycolytic enzyme essential for parasite survival and has been considered an interesting target for the development of new antichagasic compounds. The homodimeric enzyme is catalytically active only as a dimer. Interestingly, significant differences exist between the human and parasite TIMs interfaces with a sequence identity of 52%. In the present work, the binding modes of 1,2,4-thiadiazol, phenazine and 1,2,6-thiadiazine derivatives to TcTIM were investigated using molecular docking combined with molecular dynamics (MD) simulations.

Mechanistic insights from molecular dynamic simulation of Rv0045c esterase in Mycobacterium tuberculosis

Durairaj Sherlin, Sharmila Anishetty [Anna University, Chennai]

J. Mol. Mod., **21**, 90, 2015.

Rv0045c is an esterase involved in lipid metabolism of *Mycobacterium tuberculosis*. It belongs to the α/β hydrolase family. In the current study, we performed sequence- and structure-based analysis of Rv0045c followed by molecular dynamics (MD) simulation for 100 ns to investigate conformational changes in the enzyme. Sequence analysis revealed that this enzyme is possibly a hormone-sensitive lipase. Further, through structural analysis, a putative catalytic tetrad containing "Ser-Asp-Ser-His" and residues involved in the formation of an oxyanion hole were identified. MD simulation of Rv0045c revealed a conformational transition from an open to a closed state. The active site pocket was found to be gated by four loops.

Molecular dynamics study of the inhibitory effects of ChEMBL474807 on the enzymes GSK-3 β and CDK-2

Przemysław Czeleń [Nicolaus Copernicus University], Beata Szeffler

J. Mol. Mod., **21**, 74, 2015.

Indirubin derivatives and analogs comprise a significant group of ATP-competitive inhibitors. The inhibitory effects of ChEMBL474807 (1-(4-amino-1,2,5-oxadiazol-3-yl)-5-(piperidin-1-ylmethyl)-N'-(pyridin-4-ylmethylene)-1H-1,2,3-triazole-4-carbohydrazide) on two enzymes, namely glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinase-2 (CDK-2), were analyzed. The close resemblance of the amino acid sequences of these two enzymes (with 25 % identity and 41 % similarity) explains why indirubin derivatives are inhibitors of both of the enzymes studied.

Enzyme Catalysis (Cont'd)

The effect of ligands on the thermal stability of sulfotransferases: a molecular dynamics simulation study

Pu-pu Zhang, Li Zhao, Shi-yang Long, Pu Tian [Jilin University]

J. Mol.Mod., **21**, 72, 2015.

Human cytosolic sulfotransferases (hSULTs) are important phase II metabolic enzymes. They catalyze transfer of the sulfonyl-group ($-SO_3$) from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to the hydroxyl or primary amine moieties of a large number of endogenous and xenobiotic substrates. Broad selectivity and specificity of binding and activity within the sulfotransferases family could be detected by thermal denaturation assays, which have been made more and more suitable for high throughput screening based on recent technical advances. Here molecular dynamics simulations were used to explore the effect of the cofactor (PAPS) and substrate (LCA) on the thermal stability of the enzyme.

Computational study of missense mutations in phenylalanine hydroxylase

Kamila Réblová [Masaryk University], Petr Kulhánek, Lenka Fajkusová

J. Mol.Mod., **21**, 70, 2015.

Hyperphenylalaninemia (HPA) is one of the most common metabolic disorders. HPA, which is transmitted by an autosomal recessive mode of inheritance, is caused by mutations of the phenylalanine hydroxylase gene. Most mutations are missense and lead to reduced protein stability and/or impaired catalytic function. To better understand the phenotype-genotype relationships, we analyzed computationally the impact of missense mutations in homozygotes stored in the BIOPKU database.

Reactive Conformation of the Active Site in the Hairpin Ribozyme Achieved by Molecular Dynamics Simulations with ϵ/ζ Force Field Reparametrizations

Vojtěch Mlýnský, Petra Kührová, Marie Zgarbová, Petr Jurečka, Nils G. Walter, Michal Otyepka, Jiří Šponer, and Pavel Banáš [Palacky University]

J. Phys. Chem. B., **119**, 4220–4229, 2015.

X-ray crystallography can provide important insights into the structure of RNA enzymes (ribozymes). However, the details of a ribozyme's active site architecture are often altered by the inactivating chemical modifications necessary to inhibit self-cleavage. Molecular dynamics (MD) simulations are able to complement crystallographic data and model the conformation of the ribozyme's active site in its native form. However, the performance of MD simulations is driven by the quality of the force field used.

Exploring Reaction Pathways for O-GlcNAc Transferase Catalysis. A String Method Study

Manju Kumari, Stanislav Kozmon, Petr Kulhánek, Jakub Štěpán, Igor Tvaroška, and Jaroslav Koča [Masaryk University, Kamenice 5]

J. Phys. Chem. B., **119**, 4371–4381, 2015.

The inverting O-GlcNAc glycosyltransferase (OGT) is an important post-translation enzyme, which catalyzes the transfer of N-acetylglucosamine from UDP-N-acetylglucosamine (UDP-GlcNAc) to the hydroxyl group of the Ser/Thr of cytoplasmic, nuclear, and mitochondrial proteins. In the past, three different catalytic bases were proposed for the reaction: His498, α -phosphate, and Asp554. In this study, we used hybrid quantum mechanics/molecular mechanics (QM/MM) Car-Parrinello molecular dynamics to investigate reaction paths using α -phosphate and Asp554 as the catalytic bases.

Enzyme Catalysis (Cont'd)

Substrate tunnels in enzymes: Structure–function relationships and computational methodology

Laura J. Kingsley and Markus A. Lill [College of Pharmacy, Purdue University]

Proteins: Stru. Fun. & Bioinf., **83**, 599–611, 2015.

In enzymes, the active site is the location where incoming substrates are chemically converted to products. In some enzymes, this site is deeply buried within the core of the protein, and, in order to access the active site, substrates must pass through the body of the protein via a tunnel. In many systems, these tunnels act as filters and have been found to influence both substrate specificity and catalytic mechanism. The goal of this review is to outline how tunnels influence substrate specificity and catalytic efficiency in enzymes with buried active sites and to provide a brief summary of the computational tools used to identify and evaluate these tunnels.

Molecular dynamics investigation of the ionic liquid/enzyme interface: Application to engineering enzyme surface charge

Patrick R. Burney, Erik M. Nordwald, Katie Hickman, Joel L. Kaar and Jim Pfaendtner [University of Washington, Seattle]

Proteins: Stru. Fun. & Bioinf., **83**, 670–680, 2015.

Molecular simulations of the enzymes *Candida rugosa* lipase and *Bos taurus* α -chymotrypsin in aqueous ionic liquids 1-butyl-3-methylimidazolium chloride and 1-ethyl-3-methylimidazolium ethyl sulfate were used to study the change in enzyme–solvent interactions induced by modification of the enzyme surface charge. The enzymes were altered by randomly mutating lysine surface residues to glutamate, effectively decreasing the net surface charge by two for each mutation. These mutations resemble succinylation of the enzyme by chemical modification, which has been shown to enhance the stability of both enzymes in ILs.

Protein-Protein Interactions

Virtual Screening Using Combinatorial Cyclic Peptide Libraries Reveals Protein Interfaces Readily Targetable by Cyclic Peptides

Fergal J. Duffy, Darragh O'Donovan, Marc Devocelle, Niamh Moran, David J. O'Connell, and Denis C. Shields [University College Dublin]

J.Chem. Infor. and Mod. **55**, 600–613, 2015.

Protein–protein and protein–peptide interactions are responsible for the vast majority of biological functions in vivo, but targeting these interactions with small molecules has historically been difficult. What is required are efficient combined computational and experimental screening methods to choose among a number of potential protein interfaces worthy of targeting lead macrocyclic compounds for further investigation. To achieve this, we have generated combinatorial 3D virtual libraries of short disulfide-bonded peptides and compared them to pharmacophore models of important protein–protein and protein–peptide structures, including short linear motifs (SLiMs), protein-binding peptides, and turn structures at protein–protein interfaces, built from 3D models available in the Protein Data Bank.

Protein - Protein Interactions (Cont'd)

Inferring the microscopic surface energy of protein–protein interfaces from mutation data

Iain H. Moal, Justas Dapkūnas and Juan Fernández-Recio [Barcelona Supercomputing Center]

Proteins: Stru. Fun. & Bioinf., **83**, 640–650, 2015.

Mutations at protein–protein recognition sites alter binding strength by altering the chemical nature of the interacting surfaces. We present a simple surface energy model, parameterized with empirical $\Delta\Delta G$ values, yielding mean energies of $-48 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ for interactions between hydrophobic surfaces, -51 to $-80 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ for surfaces of complementary charge, and 66 – $83 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ for electrostatically repelling surfaces, relative to the aqueous phase. This places the mean energy of hydrophobic surface burial at $-24 \text{ cal mol}^{-1} \text{ \AA}^{-2}$.

Protein models docking benchmark 2

Ivan Anishchenko, Petras J. Kundrotas, Alexander V. Tuzikov and Ilya A. Vakser [The University of Kansas, Lawrence]

Proteins: Stru. Fun. & Bioinf., **83**, 891–897, 2015.

Structural characterization of protein–protein interactions is essential for our ability to understand life processes. However, only a fraction of known proteins have experimentally determined structures. Such structures provide templates for modeling of a large part of the proteome, where individual proteins can be docked by template-free or template-based techniques. We present a major update of the previously developed benchmark set of protein models. For each interactor, six models were generated with the model-to-native C α RMSD in the 1 to 6 Å range.

Membrane Proteins and Lipid Peptide Interactions

LigDig: a web server for querying ligand–protein interactions

Jonathan C. Fuller [Heidelberg Institute for Theoretical Studies (HITS)], Michael Martinez, Stefan Henrich, Antonia Stank, Stefan Richter, and Rebecca C. Wade

Bioinformatics. **31**, 1147–1149, 2015.

LigDig is a web server designed to answer questions that previously required several independent queries to diverse data sources. It also performs basic manipulations and analyses of the structures of protein–ligand complexes. The LigDig webserver is modular in design and consists of seven tools, which can be used separately, or via linking the output from one tool to the next, in order to answer more complex questions.

Capsaicin Interaction with TRPV1 Channels in a Lipid Bilayer: Molecular Dynamics Simulation

Sonya M. Hanson, Simon Newstead, Kenton J. Swartz, Mark S.P. Sansom [University of Oxford, Oxford]

Biophysical Journal. **108**, 1425–1434, 2015.

Transient receptor potential vanilloid subtype 1 (TRPV1) is a heat-sensitive ion channel also involved in pain sensation, and is the receptor for capsaicin, the active ingredient of hot chili peppers. The recent structures of TRPV1 revealed putative ligand density within the S1 to S4 voltage-sensor-like domain of the protein. However, questions remain regarding the dynamic role of the lipid bilayer in ligand binding to TRPV1. Molecular dynamics simulations were used to explore behavior of capsaicin in a 1-palmitoyl-2-oleoyl phosphatidylcholine bilayer and with the target S1–S4 transmembrane helices of TRPV1. Equilibrium simulations reveal a preferred interfacial localization for capsaicin.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Analysis of the flexibility and stability of the structure of magainin in a bilayer, and in aqueous and nonaqueous solutions using molecular dynamics simulations

ElhamEsmaili, Mohsen Shahlaei [Kermanshah University of Medical Sciences]

J. Mol.Mod., **21**, 73, 2015.

The precise mode of the antimicrobial activity of Magainin (Mag)—an antimicrobial peptide (AMP)—is still unclear. In this study, the conformation of Mag was characterized in water, and in a methanol and lipid bilayer [palmitoyl-oleoylphosphatidylcholine (POPC)] using a molecular dynamics (MD) simulation technique. To describe the role conformation plays in Mag function, the global conformational differences within three systems were studied. Through analysis of the resulting configuration ensembles, the differences in the three systems, such as overall flexibility and average secondary structure, were studied.

Classification of Current Scoring Functions

Jie Liu and Renxiao Wang [Chinese Academy of Sciences, Shanghai]

J.Chem. Infor. and Mod. **55**, 475–482, 2015.

Scoring functions are a class of computational methods widely applied in structure-based drug design for evaluating protein–ligand interactions. Dozens of scoring functions have been published since the early 1990s. In literature, scoring functions are typically classified as force-field-based, empirical, and knowledge-based. This classification scheme has been quoted for more than a decade and is still repeatedly quoted by some recent publications. Unfortunately, it does not reflect the recent progress in this field.

Strong Nonadditivity as a Key Structure–Activity Relationship Feature: Distinguishing Structural Changes from Assay Artifacts

Christian Kramer [Leopold-Franzens University Innsbruck], Julian E. Fuchs, and Klaus R. Liedl

J.Chem. Infor. and Mod. **55**, 483–494, 2015.

Nonadditivity in protein–ligand affinity data represents highly instructive structure–activity relationship (SAR) features that indicate structural changes and have the potential to guide rational drug design. In this contribution, we lay the statistical framework for systematic analysis of nonadditivity in a SAR series. First, we develop a general metric to quantify nonadditivity. Then, we demonstrate the non-negligible impact of experimental uncertainty that creates apparent nonadditivity, and we introduce techniques to handle experimental uncertainty.

Evaluating Force Fields for the Computational Prediction of Ionized Arginine and Lysine Side-Chains Partitioning into Lipid Bilayers and Octanol

Delin Sun, Jan Forsman, and Clifford E. Woodward [University of New South Wales]

J. Chem. Theor. and Comp., **11**, 1775–1791, 2015.

Abundant peptides and proteins containing arginine (Arg) and lysine (Lys) amino acids can apparently permeate cell membranes with ease. However, the mechanisms by which these peptides and proteins succeed in traversing the free energy barrier imposed by cell membranes remain largely unestablished. Precise thermodynamic studies (both theoretical and experimental) on the interactions of Arg and Lys residues with model lipid bilayers can provide valuable clues to the efficacy of these cationic peptides and proteins. We have carried out molecular dynamics simulations to calculate the interactions of ionized Arg and Lys side-chains with the zwitterionic DPPC lipid bilayer for 10 widely used lipid/protein force fields.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Investigating the Order Parameters of Saturated Lipid Molecules under Various Curvature Conditions on Spherical Supported Lipid Bilayers

Lauren E. Marbella [University of Pittsburgh, Pittsburgh],
Bocheng Yin, and Megan M. Spence

J. Phys. Chem. B., **119**, 4194–4202, 2015.

The conformations and motions of lipid molecules under different membrane curvatures have important implications for transmembrane protein function, binding events, and overall membrane organization. This work reports on the local order parameters of saturated lipid molecules, as measured by ^{13}C NMR relaxation, under several curvature conditions to probe structural changes as a function of lipid bilayer curvature. Different curvature conditions are created by depositing phosphatidylcholine membranes on spherical beads of various diameters.

Spontaneous Adsorption of Coiled-Coil Model Peptides K and E to a Mixed Lipid Bilayer

Kristyna Pluhackova, Tsjerk A. Wassenaar, Sonja Kirsch, and
Rainer A. Böckmann [University of Erlangen-Nürnberg]

J. Phys. Chem. B., **119**, 4396–4408, 2015.

A molecular description of the lipid–protein interactions underlying the adsorption of proteins to membranes is crucial for understanding, for example, the specificity of adsorption or the binding strength of a protein to a bilayer, or for characterizing protein-induced changes of membrane properties. In this paper, we extend an automated in silico assay (DAFT) for binding studies and apply it to characterize the adsorption of the model fusion peptides E and K to a mixed phospholipid/cholesterol membrane using coarse-grained molecular dynamics simulations. In addition, we couple the coarse-grained protocol to reverse transformation to atomistic resolution, thereby allowing to study molecular interactions with high detail.

Insertion Mechanism and Stability of Boron Nitride Nanotubes in Lipid Bilayers

Michael Thomas, Marta Enciso, and Tamsyn A. Hilder
[Australian National University, Canberra]

J. Phys. Chem. B., **119**, 4929–4936, 2015.

We provide insight into the interaction of boron nitride nanotubes (BNNTs) with cell membranes to better understand their improved biocompatibility compared to carbon nanotubes (CNTs). Contrary to CNTs, no computational studies exist investigating the insertion mechanism and stability of BNNTs in membranes. Our molecular dynamics simulations demonstrate that BNNTs are spontaneously attracted to lipid bilayers and are stable once inserted. They insert via a lipid-mediated, passive insertion mechanism.

Computational modeling of the N-terminus of the human dopamine transporter and its interaction with PIP₂-containing membranes

George Khelashvili [Weill Cornell Medical College of Cornell University], MilkaDoktorova, Michelle A. Sahai, NiklausJohner, Lei Shi and Harel Weinstein

Proteins: Stru. Fun. & Bioinf., **83**, 952–969, 2015.

The dopamine transporter (DAT) is a transmembrane protein belonging to the family of neurotransmitter:sodium symporters (NSS). Members of the NSS are responsible for the clearance of neurotransmitters from the synaptic cleft, and for their translocation back into the presynaptic nerve terminal. The DAT contains long intracellular N- and C-terminal domains that are strongly implicated in the transporter function. The N-terminus (N-term), in particular, regulates the reverse transport (efflux) of the substrate through DAT.

Protein Folding

Environmental polarity induces conformational transitions in a helical peptide sequence from bacteriophage T4 lysozyme and its tandem duplicate: a molecular dynamics simulation study

Harpreet Kaur, Yellamraju U. Sasidhar [Indian Institute of Technology Bombay]

J. Mol.Mod., **21**, 88, 2015.

Our recent molecular dynamics (MD) simulation of an insertion/duplication mutant 'L20' of bacteriophage T4 lysozyme demonstrated a solvent induced $\alpha \rightarrow \beta$ transition in a loosely held duplicate helical region, while α -helical conformation in the parent region was relatively stabilized by its tertiary interactions with the neighboring residues. . In this study we investigate the conformational preference of the 'parent' and 'duplicate' sequences, sans the protein context, in pure water and an apolar TFE/water solution. Apolar TFE/water solution is a model for non-polar protein context.

Reduced alphabet for protein folding prediction

Jitao T. Huang[Nankai University, Tianjin], Titi Wang, Shanran R. Huang and Xin Li

Proteins: Stru. Fun. & Bioinf., **83**, 631–639, 2015.

What are the key building blocks that would have been needed to construct complex protein folds? This is an important issue for understanding protein folding mechanism and guiding de novo protein design. Twenty naturally occurring amino acids and eight secondary structures consist of a 28-letter alphabet to determine folding kinetics and mechanism. Here we predict folding kinetic rates of proteins from many reduced alphabets. We find that a reduced alphabet of 10 letters achieves good correlation with folding rates, close to the one achieved by full 28-letter alphabet.

Unraveling the Folding Mechanism of the Smallest Knotted Protein, MJ0366

Iren Wang, Szu-Yu Chen, and Shang-Te Danny Hsu [Academia Sinica]

J. Phys. Chem. B., **119**, 4359–4370, 2015.

Understanding the mechanism by which polypeptide chains thread themselves into topologically knotted structures has emerged to be a challenging subject not least because of the additional complexity associated with the spontaneous and efficient knotting and folding events. While recent theoretical calculations have made significant progress in establishing the atomistic folding pathways for a number of knotted proteins, experimental data on the folding stabilities and kinetic pathways of knotted proteins has been sparse.

Unfolding and Folding Internal Friction of β -Hairpins Is Smaller than That of α -Helices

Julius C. F. Schulz, Markus S. Miettinen, and R. R. Netz [Freie Universität Berlin]

J. Phys. Chem. B., **119**, 4565–4574, 2015.

By the forced unfolding of polyglutamine and polyalanine homopeptides in competing α -helix and β -hairpin secondary structures, we disentangle equilibrium free energetics from nonequilibrium dissipative effects. We find that α -helices are characterized by larger friction or dissipation upon unfolding, regardless of whether they are free energetically preferred over β -hairpins or not. Our analysis, based on MD simulations for atomistic peptide models with explicit water, suggests that this difference is related to the internal friction and mostly caused by the different number of intrapeptide hydrogen bonds in the α -helix and β -hairpin states.

Protein-Nucleic acid Interactions

Molecular Dynamics Study of the Recognition of DimethylatedCpG Sites by MBD1 Protein

Caterina Bianchi and Ronen Zangi [University of the Basque Country UPV/EHU]

J.Chem. Infor. and Mod. **55**, 636–644, 2015.

The cell is able to regulate which genes to express via chemical marks on the DNA and on the histone proteins. In all vertebrates, the modification on the DNA is methylation at position 5 of the two cytosines present in the dinucleotide sequence CpG. The information encoded by these chemical marks on the DNA is processed by a family of protein factors containing a conserved methyl-CpG binding domain (MBD). Essential to their function, the MBD proteins are able to bind DNA containing dimethylatedCpG sites, whereas binding to unmethylated sites is not observed. In this paper, we perform molecular dynamics simulations to investigate the mechanism by which the mCpG binding domain of MBD1 is able to bind specifically dimethylatedCpG sites.

Physics-Based Potentials for Coarse-Grained Modeling of Protein–DNA Interactions

Yanping Yin, Adam K. Sieradzian, Adam Liwo, Yi He, and Harold A. Scheraga [Cornell University, Ithaca]

J. Chem. Theor. and Comp. **11**, 1792–1808, 2015.

Physics-based potentials have been developed for the interactions between proteins and DNA for simulations with the UNRES + NARES-2P force field. The mean-field interactions between a protein and a DNA molecule can be divided into eight categories: (1) nonpolar side chain–DNA base, (2) polar uncharged side chain–DNA base, (3) charged side chain–DNA base, (4) peptide group–phosphate group, (5) peptide group–DNA base, (6) nonpolar side chain–phosphate group, (7) polar uncharged side chain–phosphate group, and (8) charged side chain–phosphate group.

Large-Scale Quantitative Assessment of Binding Preferences in Protein–Nucleic Acid Complexes

DávidJakubec, JiříHostaš, Roman A. Laskowski, Pavel Hobza, and JiříVondrášek [Institute of Organic Chemistry and Biochemistry, Flemingovonáměstí 2]

J. Chem. Theor. and Comp. **11**, 1939–1948, 2015.

The growing number of high-quality experimental (X-ray, NMR) structures of protein–DNA complexes has sufficient enough information to assess whether universal rules governing the DNA sequence recognition process apply. While previous studies have investigated the relative abundance of various modes of amino acid–base contacts (van der Waals contacts, hydrogen bonds), relatively little is known about the energetics of these noncovalent interactions. In the present study, we have performed the first large-scale quantitative assessment of binding preferences in protein–DNA complexes by calculating the interaction energies in all 80 possible amino acid–DNA base combinations.

All-Atomic Simulations on Human Telomeric G-Quadruplex DNA Binding with Thioflavin T

Di Luo and Yuguang Mu [Nanyang Technological University]

J. Phys. Chem. B. **119**, 4955–4967, 2015.

Ligand-stabilized human telomeric G-quadruplex DNA is believed to be an anticancer agent, as it can impede the continuous elongation of telomeres by telomerase in cancer cells. In this study, five well-established human telomeric G-quadruplex DNA models were probed on their binding behaviors with thioflavin T (ThT) via both conventional molecular dynamics (MD) and well-tempered metadynamics (WT-MetaD) simulations. Novel dynamics and characteristic binding patterns were disclosed by the MD simulations.

Nucleic Acids

Rclick: a web server for comparison of RNA 3D structures

Minh N. Nguyen[Biomolecular Modeling and Design Division, Singapore] and Chandra Verma

Bioinformatics. **31**, 966-968, 2015.

RNA molecules play important roles in key biological processes in the cell and are becoming attractive for developing therapeutic applications. Since the function of RNA depends on its structure and dynamics, comparing and classifying the RNA 3D structures is of crucial importance to molecular biology. In this study, we have developed Rclick, a web server that is capable of superimposing RNA 3D structures by using clique matching and 3D least-squares fitting. Our server Rclick has been benchmarked and compared with other popular servers and methods for RNA structural alignments. In most cases, Rclick alignments were better in terms of structure overlap.

Competition among Li⁺, Na⁺, K⁺, and Rb⁺ Monovalent Ions for DNA in Molecular Dynamics Simulations Using the Additive CHARMM36 and Drude Polarizable Force Fields

Alexey Savelyev and Alexander D. MacKerell, Jr. [University of Maryland]

J. Phys. Chem. B., **119**, 4428–4440, 2015.

In the present study we report on interactions of and competition between monovalent ions for two DNA sequences in MD simulations. Efforts included the development and validation of parameters for interactions among the first-group monovalent cations, Li⁺, Na⁺, K⁺, and Rb⁺, and DNA in the Drude polarizable and additive CHARMM36 force fields (FF). The optimization process targeted gas-phase QM interaction energies of various model compounds with ions and osmotic pressures of bulk electrolyte solutions of chemically relevant ions.

Human Telomeric RNA G-Quadruplex Response to Point Mutation in the G-Quartets

Prachi Agarwala, Santosh Kumar, Satyaprakash Pandey, and Souvik Maiti [Academy of Scientific and Innovative Research (AcSIR), Anusandhan Bhawan]

J. Phys. Chem. B., **119**, 4617–4627, 2015.

Many putative G-quadruplex forming sequences have been predicted to exist in the human genome and transcriptome. As these sequences are subject to point mutations or SNPs (single nucleotide polymorphisms) during the course of evolution, we attempt to understand impact of these mutations in context of RNA G-quadruplex formation using human telomeric RNA (TERRA) as a model sequence. Our studies suggest that G-quadruplex stability is sensitive to substitution of the guanines comprising G-quartets.

Measurements of Single Nucleotide Electronic States as Nanoelectronic Fingerprints for Identification of DNA Nucleobases, Their Protonated and Unprotonated States, Isomers, and Tautomers

Josep Casamada Ribot, Anushree Chatterjee, and Prashant Nagpal [University of Colorado, Boulder]

J. Phys. Chem. B., **119**, 4968–4974, 2015.

Several nanoelectronic techniques have been explored to distinguish the sequence of nucleic acids in DNA macromolecules. Identification of unique electronic signatures using nanopore conductance, tunneling spectroscopy, or other nanoelectronic techniques depends on electronic states of the DNA nucleotides. While several experimental and computational studies have focused on interaction of nucleobases with different substrates, the effect of nucleic acid biochemistry on its electronic properties has been largely unexplored. Here, we present correlated measurements of frontier molecular orbitals and higher-order electronic states for four DNA nucleobases, and first-principle quantum chemical density functional theoretical (DFT) computations.

2. METHODOLOGY

Potentials and Parameters

Characterization of the flexible lip regions in bacteriophage lambda lysozyme using MD simulations

Lorna J. Smith [University of Oxford], Wilfred F. van Gunsteren, Niels Hansen

Eur.Biophy., **44**, 235-247, 2015.

The upper and lower lip regions in lysozyme from bacteriophage lambda (λ -lysozyme) are flexible in solution and exhibit two different conformations in crystal structures of the protein. MD simulations have been used to characterize the structure and dynamics of these lip regions, which surround the active site. Ten different simulations have been run including those with restraining to experimental NOE distance and ^1H - ^{15}N order parameter data. The simulations show that the lower lip region, although undergoing considerable backbone fluctuations, contains two persistent β -strands.

Benchmark of Schemes for Multiscale Molecular Dynamics Simulations

N. Goga, M. N. Melo, A. J. Rzepiela, A. H. de Vries, A. Hadar, S. J. Marrink [University of Groningen, Nijenborgh 7], and H. J. C. Berendsen

J. Chem. Theor. and Comp, **11**, 1389–1398, 2015.

In multiscale molecular dynamics simulations the accuracy of detailed models is combined with the efficiency of a reduced representation. For several applications — namely those of sampling enhancement — it is desirable to combine fine-grained (FG) and coarse-grained (CG) approaches into a single hybrid approach with an adjustable mixing parameter. We present a benchmark of three algorithms that use a mixing of the two representation layers using a Lagrangian formalism. The three algorithms use three different approaches for keeping the particles at the FG level of representation together: 1) addition of forces, 2) mass scaling, and 3) temperature scaling.

Molecular Dynamics

Interaction of Zn^{2+} Ions with Single-Stranded PolyU and PolyC in Neutral Solutions

V. A. Sorokin, E. L. Usenko, V. A. Valeev, Ekaterina G. Berezniak, and V. V. Andrushchenko [Academy of Sciences, Flemingovo náměstí 2]

J. Phys. Chem. B., **119**, 4409–4416, 2015.

Effect of Zn^{2+} ions on the conformation of single-stranded polynucleotides polyU and polyC in a wide temperature range at pH 7 was studied by differential UV spectroscopy and by thermal denaturation. The atoms coordinating Zn^{2+} ions were determined (O4 and N3 in polyU and N3 in polyC). A three-dimensional phase diagram and its two-dimensional components were constructed for a polyC– Zn^{2+} system. The phase diagram revealed a region in which ordered single-stranded structures, stabilized by Zn^{2+} -mediated cross-links involving N3 atom of cytosine, are formed.

Molecular Dynamics (Cont'd)

Time and Frequency-Domain Measurement of Ground-State Recovery Times in Red Fluorescent Proteins

Premashis Manna and Ralph Jimenez [University of Colorado at Boulder]

J. Phys. Chem. B., **119**, 4944–4954, 2015.

The field of bioimaging and biosensors has been revolutionized by the discovery of fluorescent proteins (FPs) and their use in live cells. FPs are characterized with rich photodynamics due to the presence of nonfluorescent or dark states which are responsible for fluorescence intermittency or “blinking”, which has been exploited in several localization-based super-resolution techniques that surpass the diffraction-limited resolution of conventional microscopy. In this work, we demonstrate time- and frequency-domain methods for the measurement of the ground-state recovery (GSR) times of FPs both in live cells and in solutions.

Free Energy Perturbation

Oxidation of Cholesterol Does Not Alter Significantly Its Uptake into High-Density Lipoprotein Particles

Topi Karilainen, Štěpán Timr, Ilpo Vattulainen, and Pavel Jungwirth [Tampere University of Technology]

J. Phys. Chem. B., **119**, 4594–4600, 2015.

Using replica exchange umbrella sampling we calculated free energy profiles for uptake of cholesterol and one of its oxysterols (7-ketocholesterol) from an aqueous solution into a high-density lipoprotein particle. These atomistic molecular dynamics simulations show that both sterols are readily taken up from the aqueous solution with comparable free energy minima at the surface of the particle of −17 kcal/mol for cholesterol and −14 kcal/mol for 7-ketocholesterol. Moreover, given its preferred position at the particle surface, 7-ketocholesterol is expected to be able to participate directly in biological signaling processes.

QM and QM/MM

The adaptive buffered force QM/MM method in the CP2K and AMBER software packages

LetifMones [University of Cambridge], Andrew Jones, Andreas W. Götz, Teodoro Laino, Ross C. Walker, Ben Leimkuhler, Gábor Csányi and Noam Bernstein

J. Comp. Chem., **36**, 633–648, 2015.

The implementation and validation of the adaptive buffered force (AdBF) quantum-mechanics/molecular-mechanics (QM/MM) method in two popular packages, CP2K and AMBER are presented. The implementations build on the existing QM/MM functionality in each code, extending it to allow for redefinition of the QM and MM regions during the simulation and reducing QM-MM interface errors by discarding forces near the boundary according to the buffered force-mixing approach. New adaptive thermostats, needed by force-mixing methods, are also implemented.

A DFT study on Cu(I) coordination in Cu-ZSM-5: Effects of the functional choice and tuning of the ONIOM approach

Simone Morpurgo [Università degli Studi di Roma “La Sapienza”]

J. Comp. Chem., **36**, 660–669, 2015.

The coordination of Cu⁺ at the T1 and T7 positions of the M7 ring of Cu-ZSM-5, and the interaction of NO with coordinated Cu⁺ were investigated by means of DFT/ONIOM calculations. The B3LYP, BLYP, PBE1PBE, PBE, M06, and M062X functionals with the def2-TZVP (def2-QZVP for Cu) basis set were used in the high-level part of ONIOM calculations, with the HF/3-21G, B3LYP/LANL2DZ, M06/LANL2DZ, and M062X/LANL2DZ methods in the low-level part.

QM and QM/MM (Cont'd)

Quantum Mechanics/Molecular Mechanics Modeling of Covalent Addition between EGFR–Cysteine 797 and N-(4-Anilinoquinazolin-6-yl) Acrylamide

Luigi Capoferri, Alessio Lodola, Silvia Rivara, and Marco Mor [Università degli Studi di Parma]

J. Chem. Infor. and Mod. **55**, 589–599, 2015.

Irreversible epidermal growth factor receptor (EGFR) inhibitors can circumvent resistance to first-generation ATP-competitive inhibitors in the treatment of non-small-cell lung cancer. They covalently bind a noncatalytic cysteine (Cys797) at the surface of EGFR active site by an acrylamide warhead. Herein, we used a hybrid quantum mechanics/molecular mechanics (QM/MM) potential in combination with umbrella sampling in the path-collective variable space to investigate the mechanism of alkylation of Cys797 by the prototypical covalent inhibitor N-(4-anilinoquinazolin-6-yl) acrylamide.

Evaluating the Potential of Halogen Bonding in Molecular Design: Automated Scaffold Decoration Using the New Scoring Function XBScore

Markus O. Zimmermann, Andreas Lange, and Frank M. Boeckler [Eberhard-Karls-University Tübingen]

J. Chem. Infor. and Mod. **55**, 687–699, 2015.

We present a QM-derived empirical scoring function for the interaction between aromatic halogenated ligands and the carbonyl oxygen atom of the protein backbone. Applying this scoring function, we developed an algorithm that evaluates the potential of protein-bound ligands to form favorable halogen-bonding contacts upon scaffold decoration with chlorine, bromine, or iodine. Full recovery of all existing halogen bonds in the PDB involving the protein backbone was achieved with our protocol. Interestingly, the potential for introducing halogen bonds through scaffold decoration of unsubstituted aromatic carbon atoms appears to easily match the number of previously known halogen bonds.

Why Do Mixed Quantum-Classical Methods Describe Short-Time Dynamics through Conical Intersections So Well? Analysis of Geometric Phase Effects

Rami Gherib, Ilya G. Ryabinkin, and Artur F. Izmaylov [University of Toronto Scarborough]

J. Chem. Theor. and Comp. **11**, 1375–1382, 2015.

Adequate simulation of nonadiabatic dynamics through conical intersection requires accounting for a nontrivial geometric phase (GP) emerging in electronic and nuclear wave functions in the adiabatic representation. Popular mixed quantum-classical (MQC) methods, surface hopping and Ehrenfest, do not carry a nuclear wave function to be able to incorporate the GP into nuclear dynamics. Surprisingly, the MQC methods reproduce ultrafast interstate crossing dynamics generated with the exact quantum propagation so well as if they contained information about the GP.

Enthalpy–Entropy Compensation upon Molecular Conformational Changes

Mazen Ahmad, Volkhard Helms, Thomas Lengauer, and Olga V. Kalinina [Max Planck Institute for Informatics]

J. Chem. Theor. and Comp. **11**, 1410–1418, 2015.

The change in free energy is the dominant factor in all chemical processes; it usually encompasses enthalpy–entropy compensation (EEC). Here, we use the free energy perturbation formalism to show that EEC is influenced by the molecular conformational changes (CCs) of the entire system comprising the solute and by the already known solvent reorganization. The internal changes of enthalpy and the entropy due to CCs upon modifying the interactions (perturbation) cancel each other exactly. The CCs influence the dissipation of the modified interactions and their contributions to the free energy.

QM and QM/MM (Cont'd)

Joint Use of Bonding Evolution Theory and QM/MM Hybrid Method for Understanding the Hydrogen Abstraction Mechanism via Cytochrome P450 Aromatase

Ignacio Viciano, Patricio González-Navarrete, Juan Andrés [UniversitatJaume I], and Sergio Martí

J. Chem. Theor. and Comp, **11**, 1470–1480, 2015.

Bonding evolution theory (BET), as a combination of the electron localization function (ELF) and Thom's catastrophe theory (CT), has been coupled with quantum mechanics/molecular mechanics (QM/MM) method in order to study biochemical reaction paths. The evolution of the bond breaking/forming processes and electron pair rearrangements in an inhomogeneous dynamic environment provided by the enzyme has been elucidated. The proposed methodology is applied in an enzymatic system in order to clarify the reaction mechanism for the hydrogen abstraction of the androstenedione (ASD) substrate catalyzed by the cytochrome P450 aromatase enzyme.

Conical Intersection Optimization Using Composed Steps Inside the ONIOM(QM:MM) Scheme: CASSCF:UFF Implementation with Microiterations

Sergi Ruiz-Barragan, KeijiMorokuma, and LluísBlancafort [Universitat de Girona]

J. Chem. Theor. and Comp, **11**, 1585–1594, 2015.

Three algorithms for optimization of minimum energy conical intersections (MECI) are implemented inside an ONIOM(QM:MM) scheme combined with microiterations. The algorithms follow the composed gradient (CG), composed gradient–composed steps (CG-CS), and double Newton–Raphson-composed step (DNR-CS) schemes developed previously for purely QM optimizations. The CASSCF and UFF methods are employed for the QM and MM calculations, respectively. The algorithms are tested on a set of 14 large hydrocarbons composed of a medium-sized chromophore (fulvene, benzene, butadiene, and hexatriene) derivatized with alkyl substituents.

Polarizable QM/MM Multiconfiguration Self-Consistent Field Approach with State-Specific Corrections: Environment Effects on Cytosine Absorption Spectrum

Quansong Li, BenedettaMennucci, Michael A. Robb, LluísBlancafort, and CarlesCurutchet [Facultat de Farmàcia, Universitat de Barcelona]

J. Chem. Theor. and Comp, **11**, 1674–1682, 2015.

We present the formulation and implementation of a polarizable quantum mechanics/molecular mechanics (QM/MM) strategy to describe environment effects in multiconfiguration self-consistent field calculations. The strategy is applied to the calculation of the vertical absorption spectrum of cytosine in water. In our approach, mutual polarization of the solute and the solvent is solved self-consistently at the complete-active-space self-consistent-field (CASSCF) level, and the resulting set of charges and dipoles is used to calculate vertical excitation energies using the complete-active-space second-order perturbative (CASPT2) approach and its multistate (MS-CASPT2) variant.

QM and QM/MM (Cont'd)

Hydration of Two Cisplatin Aqua-Derivatives Studied by Quantum Mechanics and Molecular Dynamics Simulations

Andrea Melchior, Marilena Tolazzi, José Manuel Martínez, Rafael R. Pappalardo, and Enrique Sánchez Marcos [University of Seville]

J. Chem. Theor. and Comp., **11**, 1735–1744, 2015.

The hydration of the cisplatin aqua-derivatives, cis-[PtCl(H₂O)(NH₃)₂]⁺ (w-cisplatin) and cis-[Pt(H₂O)₂(NH₃)₂]²⁺ (w2-cisplatin), has been studied by means of classical molecular dynamics simulations. The new platinum complex-water interaction potential, w-cisplatin-W, has been built on the basis of the already obtained cisplatin-water interaction potential (cisplatin-W) [*J. Chem. Theory Comput.* **20139**, 4562]. That potential has been then transferred to the w2-cisplatin-W potential. The w-cisplatin and w2-cisplatin atomic charges were specifically derived from their solute's wave functions. Bulk solvent effects on the complex-water interactions have been included by means of a continuum model.

Hybrid Quantum Mechanics/Molecular Mechanics/Coarse Grained Modeling: A Triple-Resolution Approach for Biomolecular Systems

Pandian Sokkar, Eliot Boulanger, Walter Thiel, and Elsa Sanchez-Garcia [Max-Planck-Institut für Kohlenforschung]

J. Chem. Theor. and Comp., **11**, 1809–1818, 2015.

We present a hybrid quantum mechanics/molecular mechanics/coarse-grained (QM/MM/CG) multiresolution approach for solvated biomolecular systems. The chemically important active-site region is treated at the QM level. The biomolecular environment is described by an atomistic MM force field, and the solvent is modeled with the CG Martini force field using standard or polarizable (pol-CG) water. Interactions within the QM, MM, and CG regions, and between the QM and MM regions, are treated in the usual manner, whereas the CG–MM and CG–QM interactions are evaluated using the virtual sites approach. The accuracy and efficiency of our implementation is tested for two enzymes, chorismate mutase (CM) and p-hydroxybenzoate hydroxylase (PHBH).

Accuracy of Protein Embedding Potentials: An Analysis in Terms of Electrostatic Potentials

Jógvan Magnus Haugaard Olsen [École Polytechnique Fédérale de Lausanne (EPFL)], Nanna Holmgaard List, Kasper Kristensen, and Jacob Kongsted

J. Chem. Theor. and Comp., **11**, 1832–1842, 2015.

Quantum-mechanical embedding methods have in recent years gained significant interest and may now be applied to predict a wide range of molecular properties calculated at different levels of theory. To reach a high level of accuracy in embedding methods, both the electronic structure model of the active region and the embedding potential need to be of sufficiently high quality. In fact, failures in quantum mechanics/molecular mechanics (QM/MM)-based embedding methods have often been associated with the QM/MM methodology itself; however, in many cases the reason for such failures is due to the use of an inaccurate embedding potential. In this paper, we investigate in detail the quality of the electronic component of embedding potentials designed for calculations on protein biostructures.

QM and QM/MM (Cont'd)

Pushing the Limits of a Molecular Mechanics Force Field To Probe Weak CH $\cdots\pi$ Interactions in Proteins

Arghya Barman, Bruce Batiste, and Donald Hamelberg
[Georgia State University, Atlanta]

J. Chem. Theor. and Comp., **11**, 1854–1863, 2015.

The relationship among biomolecular structure, dynamics, and function is far from being understood, and the role of subtle, weak interactions in stabilizing different conformational states is even less well-known. The cumulative effect of these interactions has broad implications for biomolecular stability and recognition and determines the equilibrium distribution of the ensemble of conformations that are critical for function. We accurately capture the stabilizing effects of weak CH $\cdots\pi$ interaction using an empirical molecular mechanics force field in excellent agreement with experiments.

Reaction Mechanism of Cobalt-Substituted Homoprotocatechuate 2,3-Dioxygenase: A QM/MM Study

Lili Cao, Geng Dong, and Wenzhen Lai [Renmin University of China]

J. Phys. Chem. B., **119**, 4608–4616, 2015.

The reaction mechanisms of cobalt-substituted homoprotocatechuate 2,3-dioxygenase (Co-HPCD) with electron-rich substrate homoprotocatechuate (HPCA) and electron-poor substrate 4-nitrocatechol (4NC) were investigated by quantum mechanical/molecular mechanical (QM/MM) calculations. Our results demonstrated that the Co-O₂ adducts has doublet ground state with a Co^{III}-O₂⁻ character when 4NC was used as the substrate, in good agreement with the EPR spectroscopic experiment.

Quantitative delineation of how breathing motions open ligand migration channels in myoglobin and its mutants

Hyuntae Na and Guang Song [Iowa State University, Ames]

Proteins: Stru. Fun. & Bioinf., **83**, 757–770, 2015.

Ligand migration and binding are central to the biological functions of many proteins such as myoglobin (Mb) and it is widely thought that protein breathing motions open up ligand channels dynamically. However, how a protein exerts its control over the opening and closing of these channels through its intrinsic dynamics is not fully understood. Specifically, a quantitative delineation of the breathing motions that are needed to open ligand channels is lacking. In this work, we present and apply a novel normal mode-based method to quantitatively delineate what and how breathing motions open ligand migration channels in Mb and its mutants.

Comparative or Homology Modeling

Improving homology modeling of G-protein coupled receptors through multiple-template derived conserved inter-residue interactions

RajanChaudhari, Andrew J. Heim, Zhijun Li [University of the Sciences in Philadelphia]

J.Comp.Aided. Mol.des. **29**, 413-420, 2015.

Evidenced by the three-rounds of G-protein coupled receptors (GPCR) Dock competitions, improving homology modeling methods of helical transmembrane proteins including the GPCRs, based on templates of low sequence identity, remains an eminent challenge. Current approaches addressing this challenge adopt the philosophy of “modeling first, refinement next”. In the present work, we developed an alternative modeling approach through the novel application of available multiple templates. First, conserved inter-residue interactions are derived from each additional template through conservation analysis of each template-target pairwise alignment.

Ligand Docking

Use of Mechanistic Models to Integrate and Analyze Multiple Proteomic Datasets

Edward C. Stites [Washington University School of Medicine], Meraj Aziz, Matthew S. Creamer, Daniel D. Von Hoff, Richard G. Posner, William S. Hlavacek

Biophysical Journal. **108**, 1819-1829, 2015.

Proteins in cell signaling networks tend to interact promiscuously through low-affinity interactions. Consequently, evaluating the physiological importance of mapped interactions can be difficult. Attempts to do so have tended to focus on single, measurable physicochemical factors, such as affinity or abundance. Here, we demonstrate that measurements of protein copy numbers and binding affinities can be integrated within the framework of a mechanistic, computational model that accounts for mass action and competition. We use cell line-specific models to rank the relative importance of protein-protein interactions in the epidermal growth factor receptor (EGFR) signaling network for 11 different cell lines.

Glycans as Biofunctional Ligands for Gold Nanorods: Stability and Targeting in Protein-Rich Media

Isabel García, Ana Sánchez-Iglesias, Malou Henriksen-Lacey, Marek Grzelczak, Soledad Penadés, and Luis M. Liz-Marzán [Paseo de Miramón 182]

J. Am. Chem. Soc., **137**, 3686–3692, 2015.

Poly(ethylene glycol) (PEG) has become the gold standard for stabilization of plasmonic nanoparticles (NPs) in biofluids, because it prevents aggregation while minimizing unspecific interactions with proteins. Application of Au NPs in biological environments requires the use of ligands that can target selected receptors, even in the presence of protein-rich media. We demonstrate here the stabilizing effect of low-molecular-weight glycans on both spherical and rod-like plasmonic NPs under physiological conditions, as bench-marked against the well-established PEG ligands.

Mapping Functional Group Free Energy Patterns at Protein Occluded Sites: Nuclear Receptors and G-Protein Coupled Receptors

Sirish Kaushik Lakkaraju, Wenbo Yu, E. Prabhu Raman, Alena V. Hershfeld, Lei Fang, Deepak A. Deshpande, and Alexander D. MacKerell, Jr. [School of Pharmacy, University of Maryland]

J. Chem. Infor. and Mod. **55**, 700–708, 2015.

Occluded ligand-binding pockets (LBP) such as those found in nuclear receptors (NR) and G-protein coupled receptors (GPCR) represent a significant opportunity and challenge for computer-aided drug design. To determine free energies maps of functional groups of these LBPs, a Grand-Canonical Monte Carlo/Molecular Dynamics (GCMC/MD) strategy is combined with the Site Identification by Ligand Competitive Saturation (SILCS) methodology. SILCS-GCMC/MD is shown to map functional group affinity patterns that recapitulate locations of functional groups across diverse classes of ligands in the LBPs of the androgen (AR) and peroxisome proliferator-activated- γ (PPAR γ) NRs and the metabotropic glutamate (mGluR) and β_2 -adrenergic (β_2 AR) GPCRs.

Ligand Docking (Cont'd)

Hybrid Steered Molecular Dynamics Approach to Computing Absolute Binding Free Energy of Ligand–Protein Complexes: A Brute Force Approach That Is Fast and Accurate

Liao Y. Chen [University of Texas at San Antonio]

J. Chem. Theor. and Comp, **11**, 1928–1938, 2015.

Computing the free energy of binding a ligand to a protein is a difficult task of essential importance for which purpose various theoretical/computational approaches have been pursued. In this paper, we develop a hybrid steered MD (hSMD) method capable of resolving one ligand–protein complex within a few wall-clock days with high enough accuracy to compare with the experimental data. This hSMD approach is based on the relationship between the binding affinity and the potential of mean force (PMF) in the established literature. It involves simultaneously steering n ($n = 1, 2, 3, \dots$) centers of mass of n selected segments of the ligand using n springs of infinite stiffness.

An SH2 domain model of STAT5 in complex with phospho-peptides define “STAT5 Binding Signatures”

Eleonora Gianti, Randy J. Zauhar [University of the Sciences, 600 S. 43rd Street, Philadelphia]

J. Comp. Aided. Mol. des. **29**, 451–470, 2015.

The signal transducer and activator of transcription 5 (STAT5) is a member of the STAT family of proteins, implicated in cell growth and differentiation. STAT activation is regulated by phosphorylation of protein monomers at conserved tyrosine residues, followed by binding to phospho-peptide pockets and subsequent dimerization. STAT5 is implicated in the development of severe pathological conditions, including many cancer forms. However, nowadays a few STAT5 inhibitors are known, and only one crystal structure of the inactive STAT5 dimer is publicly available.

Effects of ligand binding upon flexibility of proteins

Burak Ercan [Koc University, Istanbul]

Proteins: Stru. Fun. & Bioinf., **83**, 805–808, 2015.

Binding of a ligand on a protein changes the flexibility of certain parts of the protein, which directly affects its function. These changes are not the same at each point, some parts become more flexible and some others become stiffer. Here, an equation is derived that gives the stiffness map for proteins. The model is based on correlations of fluctuations of pairs of points in proteins, which may be evaluated at different levels of refinement, ranging from all atom molecular dynamics to general elastic network models, including the simplest case of isotropic Gaussian Network Model.

Combining features in a graphical model to predict protein binding sites

Torsten Wierschin, Keyu Wang, Marlon Welter, Stephan Waack and Mario Stanke [University of Greifswald, Greifswald]

Proteins: Stru. Fun. & Bioinf., **83**, 844–852, 2015.

Large efforts have been made in classifying residues as binding sites in proteins using machine learning methods. The prediction task can be translated into the computational challenge of assigning each residue the label binding site or non-binding site. Observational data comes from various possibly highly correlated sources. It includes the structure of the protein but not the structure of the complex. Here, a new CRF-approach is presented that models the dependencies of residues using a general graphical structure defined as a neighborhood graph and thus our model makes fewer independence assumptions on the labels than sequential labeling approaches.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 58, May, 2015.

- 1-9 **Complete atomistic model of a bacterial cytoplasm for integrating physics, biochemistry, and systems biology**, Michael Feig [Michigan State University], Ryuhei Harada, Takaharu Mori, Isseki Yu, Koichi Takahashi, Yuji Sugita

A model for the cytoplasm of *Mycoplasma genitalium* is presented that integrates data from a variety of sources into a physically and biochemically consistent model. Based on gene annotations, core genes expected to be present in the cytoplasm were determined and a metabolic reaction network was reconstructed.

- 10-15 **A dimension map for molecular aggregates**, Cuiying Jian, Tian Tang [Water Planet Engineering, 721D, South Glasgow Avenue], SubirBhattacharjee

See Applications / Protein Dynamics.

- 16-29 **Molecular dynamics of the asymmetric dimers of EGFR: Simulations on the active and inactive conformations of the kinase domain**, NapatSongtawee, David R. Bevan, KiattaweeChoowongkamon [Faculty of Science, Kasetsart University]

See Applications / Enzyme Catalysis.

- 30-39 **Revised force-field parameters for chlorophyll-a, pheophytin-a and plastoquinone-9**, Federico Guerra, Suliman Adam, Ana-NicoletaBondar

Biological photosynthetic machineries, such as photosystem I, photosystem II, or the bacterial reaction center, use cofactor molecules that absorb light or directly participate in chemical reactions. Here we revisit the classical force field parameters for chlorophyll-a, pheophytin-a and plastoquinone-9.

- 40-49 **Molecular docking and molecular dynamics simulation studies of Trypanosomacruzi triosephosphate isomerase inhibitors. Insights into the inhibition mechanism and selectivity**, LucíaMinini, GuzmánÁlvarez, Mercedes González, Hugo Cerecetto, Alicia Merlino [Universidad de la República]

See Applications / Enzyme Catalysis.

Journal of Computational Chemistry, 36 (9), April, 2015.

- 585–596 **Accuracy assessment of the linear Poisson–Boltzmann equation and reparametrization of the OBC generalized Born model for nucleic acids and nucleic acid–protein complexes**, Federico Fogolari [Universita' di Udine], Alessandra Corazza and Gennaro Esposito

The generalized Born model in the Onufriev, Bashford, and Case (Onufriev et al., *Proteins: StructFunct Genet* 2004, 55, 383) implementation has emerged as one of the best compromises between accuracy and speed of computation. Here, we show that the linearization of the Poisson Boltzmann equation has mild effects on computed forces, and that with optimal choice of the OBC model parameters, solvation forces, essential for molecular dynamics simulations, agree well with those computed using the reference Poisson–Boltzmann model.

- 597–600 **Ab initio calculation of anion proton affinity and ionization potential for energetic ionic liquids**, Caleb Carlin and Mark S. Gordon [Iowa State University]

Developing a better understanding of the bulk properties of ionic liquids requires accurate measurements of the underlying molecular properties that help to determine the bulk behavior. Two computational methods are used in this work: second-order perturbation theory (MP2) and completely renormalized coupled cluster theory [CR-CC(2,3)], to calculate the proton affinity and ionization potential of a set of anions that are of interest for use in protic, energetic ionic liquids.

- 601–611 **Single-ended transition state finding with the growing string method**, Paul M. Zimmerman [University of Michigan]

Reaction path finding and transition state (TS) searching are important tasks in computational chemistry. Methods that seek to optimize an evenly distributed set of structures to represent a chemical reaction path are known as double-ended string methods. In this article, a single-ended growing string method (GSM) is introduced which allows for reaction path searches starting from a single structure. The method works by sequentially adding nodes along coordinates that drive bonds, angles, and/or torsions to a desired reactive outcome.

- 612–621 **van der Waals interactions are critical in Car–Parrinello molecular dynamics simulations of porphyrin–fullerene dyads**, TopiKarilainen, OanaCramariuc [Tampere University of Technology], Mikael Kuisma, KirsiTappura and Terttu I. Hukka

The interplay between electrostatic and van der Waals (vdW) interactions in porphyrin-C₆₀ dyads is still under debate despite its importance in influencing the structural characteristics of such complexes considered for various applications in molecular photovoltaics. In this article, we sample the conformational space of a porphyrin-C₆₀ dyad using Car–Parrinello molecular dynamics simulations with and without empirical vdW corrections.

- 622–632 **Accurate reaction barrier heights of pericyclic reactions: Surprisingly large deviations for the CBS-QB3 composite method and their consequences in DFT benchmark studies**, Amir Karton [The University of Western Australia] and Lars Goerigk

Accurate barrier heights are obtained for the 26 pericyclic reactions in the BHPERI dataset by means of the high-level Wn-F12 thermochemical protocols. Very often, the complete basis set (CBS)-type composite

methods are used in similar situations, but herein it is shown that they in fact result in surprisingly large errors with root mean square deviations (RMSDs) of about 2.5 kcal mol⁻¹.

- 633–648 **The adaptive buffered force QM/MM method in the CP2K and AMBER software packages**, Letif Mones [University of Cambridge], Andrew Jones, Andreas W. Götz, Teodoro Laino, Ross C. Walker, Ben Leimkuhler, Gábor Csányi and Noam Bernstein

See Methodology / QM and QM/MM.

- 649–659 **Quantifying electro/nucleophilicity by partitioning the dual descriptor**, Vincent Tognetti [Université de Rouen], Christophe Morell and Laurent Joubert

Translating local electro/nucleophilicities into the language of reactive sites is an appealing theoretical challenge that could be conducive to strengthen the collaborative dialogue between experimentalists and quantum chemists. In this article, we present instead an approach based on the dual descriptor Δf , which aims at partitioning real space into nonoverlapping reactive domains that feature a constant Δf sign.

- 660–669 **A DFT study on Cu(I) coordination in Cu-ZSM-5: Effects of the functional choice and tuning of the ONIOM approach**, Simone Morpurgo [Università degli Studi di Roma “La Sapienza”]

See Methodology / QM and QM/MM.

- 670–688 **Unitary group adapted state specific multireference perturbation theory: Formulation and pilot applications**, Avijit Sen, Sangita Sen, Pradipta Kumar Samanta and Debashis Mukherjee [Indian Association for the Cultivation of Sciences]

We present here a comprehensive account of the formulation and pilot applications of the second-order perturbative analogue of the recently proposed unitary group adapted state-specific multireference coupled cluster theory (UGA-SSMRCC), which we call as the UGA-SSMRPT2.

Journal of Computational Chemistry, 36 (10), April, 2015.

- 695–706 **Electronic structure and microscopic charge-transport properties of a new-type diketopyrrolopyrrole-based material**, Jin-Dou Huang, Wen-Liang Li, Shu-Hao Wen and Bin Dong [Dalian Nationalities University]

Recently, diketopyrrolopyrrole (DPP)-based materials have attracted much interest due to their promising performance as a subunit in organic field effect transistors. Using density functional theory and charge-transport models, we investigated the electronic structure and microscopic charge transport properties of the cyanated bithiophene-functionalized DPP molecule (compound **1**).

- 707–716 **Hydrogen–hydrogen bonding: The current density perspective**, Paolo Della Porta, Riccardo Zanasi and Guglielmo Monaco [University of Salerno]

Current density plots of closed-shell intermolecular H—H interactions characterized by a bond critical point (BCP) show two vortices separated by a saddle, a pattern which allows for a clear definition of a pair current strength. This H—H current strength turns out to be roughly related to the potential energy density at the BCP and then to the dissociation energy.

- 717–722 **Deformation of single-walled carbon nanotubes by interaction with graphene: A first-principles study**, Xiao Wang, Juan Yang, Ruoming Li, Hong Jiang and Yan Li [Peking University, Beijing]

The interaction between single-walled carbon nanotubes (SWNTs) and graphene were studied with first-principles calculations.

- 723–730 **Origin-independent sum over states simulations of magnetic and electronic circular dichroism spectra via the localized orbital/local origin method**, Petr Štěpánek and Petr Bouř [Academy of Sciences, Prague]

Although electronic and magnetic circular dichroism (ECD, MCD) spectra reveal valuable details about molecular geometry and electronic structure, quantum-chemical simulations significantly facilitate their interpretation. In this study, a more elegant way is proposed, based on the localized orbital/local origin (LORG) formalism, and a similar approach is also applied to generate ECD intensities.

- 731–738 **The multieffects of DMF and DBU on the [5 + 1] benzannulation of nitroethane and α -alkenoyl ketene-(S,S)-acetals: Hydrogen bonding and electrostatic interactions**, Haiyan Yuan, Yiying Zheng, Bo Li, Wenliang Li and Jingping Zhang [Northeast Normal University]

A density functional theory (DFT) study was performed to elucidate the mechanism for the [5 + 1] benzannulation of nitroethane and α -alkenoyl ketene-(S,S)-acetals. The calculation results are consistent with experimental findings, showing that the reaction proceeds via deprotonation of nitroethane, nucleophilic addition, intramolecular cyclization, elimination of HNO₂, and the keto-enol tautomerization sequence.

- 739–750 **On combining Thole's induced point dipole model with fixed charge distributions in molecular mechanics force fields**, Hanne S. Antila and Emppu Salonen [Aalto University]

The Thole induced point dipole model is combined with three different point charge fitting methods, Merz–Kollman (MK), charges from electrostatic potentials using a grid (CHELPG), and restrained electrostatic potential (RESP), and two multipole algorithms, distributed multipole analysis (DMA) and Gaussian multipole model (GMM), which can be used to describe the electrostatic potential (ESP) around molecules in molecular mechanics force fields.

- 751–762 **Stability of ion triplets in ionic liquid/lithium salt solutions: Insights from implicit and explicit solvent models and molecular dynamics simulations**, Andrzej Eilmes [Jagiellonian University] and Piotr Kubisiak

Binding energies of ion triplets formed in ionic liquids by Li⁺ with two anions have been studied using quantum-chemical calculations with implicit and explicit solvent supplemented by molecular dynamics (MD) simulations.

- 763–772 **Enhanced conformational sampling method for proteins based on the TaBooSeArch algorithm: Application to the folding of a mini-protein, chignolin**, Ryuhei Harada, Yu Takano and Yasuteru Shigeta [University of Tsukuba]

See Applications / Protein Conformational Analysis.

- 773–784 **How does a hydrocarbon staple affect peptide hydrophobicity?**, Adelene Y. L. Sim [Bioinformatics Institute (A*STAR)] and Chandra Verma

See Applications / Water and Solvation.

Journal of Computational Chemistry, 36 (11), April, 2015.

- 785–794 **Dividing a complex reaction involving a hypervalent iodine reagent into three limiting mechanisms by *ab initio* molecular dynamics**, Oliver Sala, Hans Peter Lüthi [Laboratorium für Physikalische Chemie], Antonio Togni, Marcella Iannuzzi and Jürg Hutter

The electrophilic *N*-trifluoromethylation of MeCN with a hypervalent iodine reagent to form a nitrilium ion, that is rapidly trapped by an azole nucleophile, is thought to occur via reductive elimination (RE). A recent study showed that, depending on the solvent representation, the S_N2 is favoured to a different extent over the RE.

- 795–804 **Can substituted allenes be highly efficient leaving groups in catalytic processes? A computational investigation**, Nishamol Kuriakose and Kumar Vanka [National Chemical Laboratory, Pune]

There is considerable interest presently in the chemistry of allenes. The current computational investigation looks into the possibility of using allenes and their derivatives as leaving groups.

- 805–815 **Bonding and singlet–triplet gap of silicon trimer: Effects of protonation and attachment of alkali metal cations**, Nguyen Minh Tam, Tran Dieu Hang, Hung Tan Pham, Huyen Thi Nguyen, My Phuong Pham-Ho, Pablo A. Denis and Minh Tho Nguyen [Institute for Computational Science and Technology (ICST), Quang Trung Software City]

We revisit the singlet–triplet energy gap (ΔE_{ST}) of silicon trimer and evaluate the gaps of its derivatives by attachment of a cation (H^+ , Li^+ , Na^+ , and K^+) using the wavefunction-based methods including the composite G4, coupled-cluster theory CCSD(T)/CBS, CCSDT and CCSDTQ, and CASSCF/CASPT2 (for Si_3) computations.

- 816–820 **An *ab initio* study of nuclear volume effects for isotope fractionations using two-component relativistic methods**, Keisuke Nemoto, Minoru Abe [Tokyo Metropolitan University], Junji Seino and Masahiko Hada

We investigate the accuracy of two-component Douglas–Kroll–Hess (DKH) methods in calculations of the nuclear volume term ($\equiv \ln K_{nv}$) in the isotope fractionation coefficient. $\ln K_{nv}$ is a main term in the chemical equilibrium constant for isotope exchange reactions in heavy element.

- 821–832 **Theoretical investigation of the halogen bonded complexes between carbonyl bases and molecular chlorine**, Wiktor Zierkiewicz [Wrocław University of Technology], Dariusz C. Bieńko, Danuta Michalska and Thérèse Zeegers-Huyskens

The halogen bonded complexes between six carbonyl bases and molecular chlorine are investigated theoretically. The interaction energies calculated at the CCSD(T)/aug-cc-pVTZ level range between -1.61 and -3.50 kcal mol $^{-1}$.

- 833–843 **One-electron images in real space: Natural adaptive orbitals**, Marcos Menéndez, Roberto Álvarez Boto, Evelio Francisco and Ángel Martín Pendás [Universidad de Oviedo]

We introduce a general procedure to construct a set of one-electron functions in chemical bonding theory, which remain physically sound both for correlated and noncorrelated electronic structure descriptions.

- 844–852 **Probing the reactivity of microhydrated α -nucleophile in the anionic gas-phase S_N2 reaction**, Wen-Yang Zhao, Jie Yu, Si-Jia Ren, Xi-Guang Wei, Fang-Zhou Qiu, Peng-Hui Li, He Li, Yi-Peng Zhou, Chang-Zhen Yin, An-Pu Chen, Hao Li, Lei Zhang, Jun Zhu, Yi Ren [Sichuan University, Chengdu] and Kai-Chung Lau

To probe the kinetic performance of microsolvated α -nucleophile, the $G2(+)_M$ calculations were carried out for the gas-phase S_N2 reactions of monohydrated and dihydrated α -oxy-nucleophiles $XO^-(H_2O)_{n=1,2}$ ($X = HO, CH_3O, F, Cl, Br$), and α -sulfur-nucleophile, $HSS^-(H_2O)_{n=1,2}$, toward CH_3Cl .

- 853–860 **Solvatochromic shifts of Br_2 and I_2 in water cages of type 5^{12} , $5^{12}6^2$, $5^{12}6^3$, and $5^{12}6^4$** , Nils Middendorf, Katharina Krause and Sebastian Höfener [Karlsruher Institut für Technologie (KIT), Karlsruhe]

Despite the relatively small size of molecular bromine and iodine, the physicochemical behavior in different solvents is not yet fully understood, in particular when excited-state properties are sought. In this work, we investigate isolated halogen molecules trapped in clathrate hydrate cages. Relativistic supermolecular calculations reveal that the environment shift to the excitation energies of the (nondegenerate) states $^3\Pi_u$ and $^1\Pi_u$ lie within a spread of 0.05 eV, respectively, suggesting that environment shifts can be estimated with scalar-relativistic treatments.

- 861–869 **Electronic reorganization triggered by electron transfer: The intervalence charge transfer of a Fe^{3+}/Fe^{2+} bimetallic complex**, Alex Domingo [Department of Chemistry, Belgium], Celestino Angeli, Coen de Graaf and Vincent Robert

The key role of the molecular orbitals in describing electron transfer processes is put in evidence for the intervalence charge transfer (IVCT) of a synthetic nonheme binuclear mixed-valence Fe^{3+}/Fe^{2+} compound.

Journal of Molecular Modeling, 21 (4), April, 2015.

- 103 **Effect of collision energy on the reaction mechanism of $C(3P) + OH(X^2\Pi) \rightarrow CO(X^1\Sigma^+) + H(^2S)$** , Yanru Huang [Liaoning Shihua University]

Quasiclassical trajectory calculations based on a fully global ab initio potential energy surface of the rotational angular momentum polarisation of the product CO in the title reaction are reported.

- 102 **In silico identification of novel kinase inhibitors by targeting B-Raf^{v600e} from natural products database**, Zi-jie Wang, Zhi-ning Wan, Xu-dong Chen, Chuan-fang Wu, Guo-long Gao, Rong Liu, Zheng Shi, Jin-ku Bao [Sichuan University, Chengdu]

See Applications / Medicinal Chemistry and Drug Design.

- 101 **Symmetric nested complexes of fullerenes**, Naveicy Mar, Luis Enrique Sansores, Stephen Muhl, Estrella Ramos, Roberto Salcedo [Universidad Nacional Autónoma de México]

Large fullerenes such as C_{180} and C_{116} can be used as hosts for other molecules of the same family. Based on this idea, two complexes were designed, one in which C_{180} accepts a C_{60} molecule as a guest and the other in which C_{20} was placed inside C_{116} .

- 100 **Molecular dynamics simulation and conformational analysis of some catalytically active peptides**, Bahareh Honarparvar [University of KwaZulu-Natal], Adam A. Skelton

See Applications / Protein Confirmation Analysis.

- 99 **The DFT local reactivity descriptors of α -tocopherol**, Ivana Fabijanić, Cvijeta Jakobušić Brala, Viktor Pilepić [University of Zagreb]

The calculations of local reactivity descriptors, the electron donor Fukui function $f^-(r)$, the average local ionization energy $\bar{I}(r)$, the Fukui function dual descriptor $f^{(2)}(r)$, and the electron acceptor Fukui function $f^+(r)$ for α -tocopherol, the main biologically active form of vitamin E for antioxidant reactions in phospholipid membranes, is presented.

- 98 **Microsolvation and hydration enthalpies of $\text{CaS}_2\text{O}_3(\text{H}_2\text{O})_n (n = 0-19)$ and $\text{S}_2\text{O}_3^{2-}(\text{H}_2\text{O})_n (n = 0-16)$: an ab initio study**, Victor M. Rosas-García [Ciudad Universitaria], Isabel del Carmen Sáenz-Tavera, María del Rosario Rojas-Unda

We studied microhydrated calcium thiosulfate and its ions at the restricted Hartree-Fock RHF/6-31G* level of theory. A semiempirical molecular dynamics search of progressively more hydrated species provided lowest-energy configurations that were then fully optimized and characterized as energy minima at the RHF/6-31G* level of theory.

- 97 **Metal coordination study at Ag and Cd sites in crown thioether complexes through DFT calculations and hyperfine parameters**, Rafael R. do Nascimento, Filipe C. D. A. Lima, Marcos B. Gonçalves, Leonardo A. Errico, Mario Rentería, Helena M. Petrilli [Cidade Universitária]

Structural and electronic properties of $[\text{C}_{12}\text{H}_{24}\text{S}_6\text{X}]$, $[\text{C}_{13}\text{H}_{26}\text{S}_6\text{OX}]$, and $[\text{C}_{14}\text{H}_{28}\text{S}_6\text{OX}]$ ($\text{X}: \text{Ag}^+, \text{Cd}^{2+}$) crown thioether complexes were investigated within the framework of the density functional theory (DFT) using the projector augmented wave (PAW) method.

- 96 **Pyrazolo[3,4-*d*]pyrimidines as novel inhibitors of O-acetyl-L-serine sulfhydrylase of *Entamoeba histolytica*: an in silico study**, Umesh Yadava [D.D.U. Gorakhpur University], Bindesh Kumar Shukla, Mihir Roychoudhury, Devesh Kumar

See Applications / Medicinal Chemistry and Drug Design.

- 95 **Carborane tuning on iridium complexes: redox-switchable second-order NLO responses**, Jiao Wang, Wen-Yong Wang, Xin-Yan Fang, Yong-Qing Qiu [Northeast Normal University, Changchun]

Much effort has been devoted to investigating the molecular geometries, electronic structures, redox properties and nonlinear optical (NLO) properties of Ir complexes involving *o*-, *m*- or *p*-carborane groups by density functional theory (DFT) methods. Our calculations revealed that oxidation reactions have a significant influence on the second-order NLO response owing to the change in charge transfer pattern.

- 94 **A computational study of intramolecular hydrogen bonds breaking/formation: impact on the structural flexibility of the ranitidine molecule**, Mariana Kozłowska [University of Białystok], Jakub Gołon, Paweł Rodziewicz

Ranitidine is a histamine H₂-receptor antagonist that reduces gastric acid secretion. We studied the flexibility of the ranitidine molecule with the special focus on the network of diverse intramolecular hydrogen bonds: N-H ...O, N-H ...N, C-H ...O, C-H ...N and N-H ...S.

- 93 **Understanding the azeotropic diethyl carbonate–water mixture by structural and energetic characterization of DEC(H₂O)_n heteroclusters**, Juan D. Ripoll, Sol M. Mejía [Pontificia Universidad Javeriana], Matthew J. L. Mills, Aída L. Villa

Diethyl carbonate (DEC) is an oxygenated fuel additive. During its synthesis through a promising green process, a DEC-water azeotrope is formed, which decreases DEC production efficiency in the gas phase. We report a detailed computational study of the conformers of DEC, and their microsolvation with up to four water molecules, with the goal of understanding the observed 1:3 DEC:H₂O molar ratio.

- 92 **Electronic effects of the substituent on the dioxygen-activating abilities of substituted iron tetraphenylporphyrins: a theoretical study**, Haiyan Fu, Meijuan Cao, Yuanbin She [Zhejiang University of Technology], Zhicheng Sun, Yanmin Yu

A density functional theoretical (DFT) method was applied to understand the effects of the substituent on dioxygen activation by a series of substituted iron tetraphenylporphyrins [FeT(*o/p*-R)PP (*o* = *ortho*-substituted, *p* = *para*-substituted; R = -H, -Cl, -NO₂, -CH₃, -OCH₃)].

- 91 **First principles simulation of temperature dependent electronic transition of FM-AFM phase BFO**, Liang Bian [Xinjiang Key Laboratory of Electronic Information Materials and Devices], Jin-bao Xu, Mian-xin Song, Fa-qin Dong, Hai-liang Dong, Fa-Nian Shi, Xiao-Yan Zhang, Tao Duan

Understanding how temperature affects the electronic transitions of BFO is important for design of BiFeO₃ (BFO)-based temperature-sensitive device. Hitherto, however, there have been only very limited reports of the quantitative simulation. Here, we used density functional theory (DFT) and two-dimensional correlation analysis (2D-CA) techniques to calculate the systematic variations in electronic transitions of BFO crystal, over a range of temperature (50~1500 K).

- 90 **Mechanistic insights from molecular dynamic simulation of Rv0045c esterase in Mycobacterium tuberculosis**, DurairajSherlin, SharmilaAnishetty [Anna University, Chennai]

See Applications / Enzyme Catalysis.

- 89 **Theoretical study of formamide decomposition pathways over (6,0) silicon-carbide nanotube**, Mehdi D. Esrafilil [University of Maragheh], MozghanGhanbari, RoghayeNurazar, ParisaNematollahi

In this study, we systematically identified possible reaction pathways for the catalytic decomposition of formamide (FM) on a (6,0) silicon-carbide nanotube surface by means of density functional theory.

- 88 **Environmental polarity induces conformational transitions in a helical peptide sequence from bacteriophage T4 lysozyme and its tandem duplicate: a molecular dynamics simulation study**, Harpreet Kaur, Yellamraju U. Sasidhar [Indian Institute of Technology Bombay]

See Applications / Protein Folding.

- 87 **Theoretical study of the Wittig reaction of cyclic ketones with phosphorus ylide**, NishaJarwal, PompozhiProtasisThankachan [Indian Institute of Technology Roorkee]

The Wittig reaction of cyclopropanone, cyclobutanone and cyclopentanone with phosphorus ylide ($\text{Me}_3\text{P} = \text{CH}_2$) in gas phase was investigated computationally at B3LYP/6-31G** level of theory.

- 86 **Theoretical study of the mechanism of highly diastereoselective formation of a strained 3-azabicyclo[3.2.0]heptane derivative**, Maryam Nemat, NematollahArshadi [University of Zanjan]

The mechanism of multicomponent reactions, especially stereoselective ones is of special importance in organic synthesis. The mechanism of diastereoselective formation of a highly strained 3-azabicyclo[3.2.0]heptane derivative through a catalyst-free multistep reaction is studied by DFT calculations in solution phase.

- 85 **Influence of GHz electric fields on the mechanical properties of a microtubule**, S. S. Setayandeh, A. Lohrasebi [University of Isfahan]

The effects of external GHz electric fields on the mechanical properties of a microtubule (MT) have been modeled through the application of a molecular dynamics simulation method.

- 84 **Conformational landscape and low lying excited states of imatinib**, Emil Vințeler, Nicoleta-Florina Stan, RalucaLuchian, CălinCăinap, João P. Prates Ramalho, VasileChiș [Babeș-Bolyai University]

The conformational changes of imatinib (IMT) are crucial for understanding the ligand–receptor interaction and its mechanism of action [Agofonov et al. (2014) Nature StructMolBiol 21:848–853]. Therefore, here we investigated the free energy conformational landscape of the free IMT base, aiming to describe the three-dimensional structures and energetic stability of its conformers.

- 83 **Pressure-imposed changes of benzoic acid crystals**, Piotr Cysewski [Nicolaus Copernicus University in Toruń]

Structural and energetic properties of benzoic acid crystals at pressure elevated from ambient condition up to 2.21 GPa were characterized. The directly observed variations of cell parameters and consequently cell volume are associated with many other changes including energetic, geometric, and electronic characteristics.

- 82 **Reactivity indices for natural bond orbitals: a new methodology**, Jesús Sánchez-Márquez [Campus Universitario Río San Pedro]

A new reactivity index has been defined; this parameter is focused on a molecule's natural bond orbitals (NBOs) and derives in a natural way from Fukui functions.

- 81 **Comparative theoretical investigation of the structures, energetics, and stabilities of $\text{C}_7\text{N}_5\text{H}_{11}$ cages**, Jianying Zhang [ChuZhou University], Xuedong Gong

Carbon-nitrogen cages are the focus of much research due to their potential use as high energy density materials (HEDMs). Several such cage isomers of $\text{C}_7\text{N}_5\text{H}_{11}$, created by modifying the most stable N_{12} cage, were examined by performing theoretical calculations to evaluate their suitability as potential HEDMs.

- 80 **The N₂O activation by Rh₅ clusters. A quantum chemistry study**, Oscar Olvera-Neria [Universidad Autónoma Metropolitana-Azcapotzalco], Roberto Avilés, Héctor Francisco-Rodríguez, Virineya Bertin, Raúl García-Cruz, Julio César González-Torres, Enrique Poulain

Nitrous oxide (N₂O) is a by-product of exhaust pipe gases treatment produced by motor vehicles. Therefore, the N₂O reduction to N₂ is necessary to meet the actual environmental legislation. The N₂O adsorption and dissociation assisted by the square-based pyramidal Rh₅ cluster was investigated using the density functional theory and the zero-order regular approximation (ZORA).

- 79 **Hylleraas hydride binding energy: diatomic electron affinities**, Edward S. Chen [Baylor College of Medicine], Herman Keith, Tristan Lim, Dang Pham, Reece Rosenthal, Charles Herder, Sunil Pai, R. A. Flores, Edward C. M. Chen

Theoretical adiabatic electron affinities are often considered inaccurate because they are referenced to only a single value. Ground state electron affinities for all the main group elements and homonuclear diatomics were identified recently using the normalized binding energy of the hydrogen atom: $[0.75420375(3)/2 = 0.37710187(1) \text{ eV}]$.

- 78 **Relative stabilities of HCl•H₂SO₄•HNO₃ aggregates in polar stratospheric clouds**, Marian Verdes [Universidad Autónoma de Madrid], M. Paniagua

Strong acids such as HCl (C), HNO₃ (N) and H₂SO₄ (S) acquire relevance in Polar Stratospheric Clouds (PSCs) and aerosols in which nucleation processes occur. Ab initio quantum chemical studies of aggregates were performed for these strong acids. Structures were calculated using DFT methods with the B3LYP hybrid functional and aug-cc-pVTZ basis set.

- 77 **The electronic mechanism ruling the dihydrogen bonds and halogen bonds in weakly bound systems of H₃SiH...HOX and H₃SiH...XOH (X = F, Cl, and Br)**, Boaz G. Oliveira [Universidade Federal da Bahia], Abedin Zabardasti, Hamid Goudarziafshar, Maryam Salehnassaj

The dihydrogen bond complexes (H₃SiH...HOX) and halogen bond complexes (H₃SiH...XOH) formed between SiH₄ and hypohalous acids HOX (X = F, Cl, and Br) have been studied at the MP2/6-311++G(2d,2p) computational level.

- 76 **Insight into the substitution reactions of silylenoid H₂SiLiF with GeH₃X (X = F, Cl, Br): a theoretical study**, Bingfei Yan, Wenzuo Li [Yantai University], Cuiping Xiao, Qingzhong Li, Jianbo Cheng

The unique substitution reactions of the three-membered-ring silylenoid H₂SiLiF with GeH₃X (X = F, Cl, Br) were investigated using ab initio and density functional theory calculations.

- 75 **A QM-MD simulation approach to the analysis of FRET processes in (bio)molecular systems. A case study: complexes of *E. coli* purine nucleoside phosphorylase and its mutants with formycin A**, M. Sobieraj, K. A. Krzyśko, A. Jarmuła, M. W. Kalinowski, B. Lesyng, M. Prokopowicz, J. Cieśla, A. Gojdz, B. Kierdaszuk [University of Warsaw]

Predicting FRET pathways in proteins using computer simulation techniques is very important for reliable interpretation of experimental data. A novel and relatively simple methodology has been developed and applied to purine nucleoside phosphorylase (PNP) complexed with a fluorescent ligand — formycin A (FA). FRET occurs between an excited Tyr residue (D*) and FA (A).

- 74 **Molecular dynamics study of the inhibitory effects of ChEMBL474807 on the enzymes GSK-3 β and CDK-2**, Przemysław Czeleń [Nicolaus Copernicus University], Beata Szeffler

See Applications / Enzyme Catalysis.

- 73 **Analysis of the flexibility and stability of the structure of magainin in a bilayer, and in aqueous and nonaqueous solutions using molecular dynamics simulations**, Elham Esmaili, Mohsen Shahlaei [Kermanshah University of Medical Sciences]

See Applications / Membrane Proteins.

- 72 **The effect of ligands on the thermal stability of sulfotransferases: a molecular dynamics simulation study**, Pu-pu Zhang, Li Zhao, Shi-yang Long, Pu Tian [Jilin University]

See Applications / Enzyme Catalysis.

- 71 **Electronic structure of modeled vs. real carbon-chain containing organometallic dinuclear complexes: similarities and differences**, Abdelkader Ladjarafi, Karine Costuas, Hacène Meghezzi, Jean-François Halet [Université de Rennes 1]

DFT calculations were carried out on the homo- and hetero-bimetallic model wires $[(\eta^5\text{-C}_5\text{H}_5)(\text{dpe})\text{Fe-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Fe}(\text{dpe})(\eta^5\text{-C}_5\text{H}_5)]$ (**1'**), $[(\eta^7\text{-C}_7\text{H}_7)(\text{dpe})\text{Mo-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Mo}(\text{dpe})(\eta^7\text{-C}_7\text{H}_7)]$ (**2'**), and $[(\eta^5\text{-C}_5\text{H}_5)(\text{dpe})\text{Fe-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Mo}(\text{dpe})(\eta^7\text{-C}_7\text{H}_7)]$ (**3'**) used to tentatively mimic $[(\eta^5\text{-C}_5\text{Me}_5)(\text{dppe})\text{Fe-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Fe}(\text{dppe})(\eta^5\text{-C}_5\text{Me}_5)]$ (**1**), $[(\eta^7\text{-C}_7\text{H}_7)(\text{dppe})\text{Mo-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Mo}(\text{dppe})(\eta^7\text{-C}_7\text{H}_7)]$ (**2**), and $[(\eta^5\text{-C}_5\text{Me}_5)(\text{dppe})\text{Fe-C}\equiv\text{C-C}_6\text{H}_4\text{-C}\equiv\text{C-Mo}(\text{dppe})(\eta^7\text{-C}_7\text{H}_7)]$ (**3**), respectively in order to analyze the similarities and the differences between models and real compounds previously theoretically and experimentally studied, with respect to their molecular structures and properties.

- 70 **Computational study of missense mutations in phenylalanine hydroxylase**, Kamila Réblová [Masaryk University], Petr Kulhánek, Lenka Fajkusová

See Applications / Enzyme Catalysis.

- 69 **Theoretical insight on atmospheric chemistry of HFE-365mcf3: reactions with OH radicals, atmospheric lifetime, and fate of alkoxy radicals ($\text{CF}_3\text{CF}_2\text{CH}(\text{O}^\bullet)\text{OCH}_3/\text{CF}_3\text{CF}_2\text{CH}_2\text{OCH}_2\text{O}^\bullet$)**, Debajyoti Bhattacharjee, Bhupesh Kumar Mishra, Ramesh Chandra Deka [Tezpur University]

In the present work, theoretical study on the mechanism and kinetics of the gas-phase reactions of $\text{CF}_3\text{CF}_2\text{CH}_2\text{OCH}_3$ (HFE-365mcf3) with the OH radicals have been performed using meta-hybrid modern density functional M06-2X in conjunction with 6-31+G(d,p) basis set.

- 68 **New insights into the insertion reactions of germylenoid H_2GeLiF with RH ($\text{R} = \text{F}, \text{OH}, \text{NH}_2$)**, Bingfei Yan, Wenzuo Li [Yantai University], Cuiping Xiao, Zhenbo Liu, Qingzhong Li, Jianbo Cheng

In the present work, a new pathway of the insertion reactions of H_2GeLiF with RH ($\text{R} = \text{F}, \text{OH}, \text{NH}_2$) was investigated using DFT B3LYP and QCISD methods.

- 67 **Computational design of small phenothiazine dyes for dye-sensitized solar cells by functionalizations affecting the thiophene unit,** Wei Han Tu [Anderson Junior College, Singapore], Yi Yin Tan, OmkarRege, Sergei Manzhos

We present a computational density functional theory study of the potential to improve the solar absorbance of small organic dyes featuring a phenothiazine donor and an acceptor moiety that combines a thiophene unit and a cyanoacrylic group.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

A. Lohrasebi
lohrasebi@nano.ipm.ac.ir
Department of Physics,
University of Isfahan,
Isfahan, Iran

Adelene Y. L. Sim
adelenes@bii.a-star.edu.sg
Bioinformatics Institute
(A*STAR),
Matrix, Singapore

Alemayehu A. Gorfe
Alemayehu.G.abebe@uth.tmc.edu
Department of Integrative Biology
and Pharmacology,
University of Texas Health Science
Center at Houston,
Houston, Texas

Alex Domingo
alex.domingotoro@chem.kuleuven
.be
Department of Chemistry,
Belgium

Alexander Bujotzek
alexander.bujotzek@roche.com
Roche Pharmaceutical Research
and Early Development,
Large Molecule Research,
Roche Innovation Center Penzberg,
Penzberg,
Germany

Alexander D. MacKerell, Jr.
alex@outerbanks.umaryland.edu
Department of Pharmaceutical
Sciences,
School of Pharmacy, University of
Maryland,
20 Penn Street, Baltimore,
Maryland 21201, United States

Alexander D. MacKerell, Jr.
alex@outerbanks.umaryland.edu.
Department of Pharmaceutical
Sciences,
School of Pharmacy, University of
Maryland,
Baltimore, Maryland 21201,
United States

Alicia Merlino
amerlino@fcien.edu.uy

Laboratorio de Química Teórica y
Computacional,
Instituto de Química Biológica,
Facultad de Ciencias, Universidad
de la República,
Iguá 4225, Montevideo 11400,
Uruguay

Amir Karton
amir.karton@uwa.edu.au
School of Chemistry and
Biochemistry,
The University of Western
Australia,
Perth, WA, Australia

Ana-Nicoleta Bondar
nbondar@zedat.fu-berlin.de

Anatoly B. Kolomeisky
tolya@rice.edu
Rice University,
Department of Chemistry and
Center for Theoretical Biological
Physics,
Houston, Texas 77005, United
States

Andrzej Eilmes
eilmes@chemia.uj.edu.pl
Jagiellonian University,
Faculty of Chemistry,
Department of Computational
Methods in Chemistry,
Kraków, Poland

Ángel Martín Pendás
angel@fluor.quimica.uniovi.es
Departamento de Química Física y
Analítica,
Facultad de Química,
Universidad de Oviedo, Spain

Artur F. Izmaylov
artur.izmaylov@utoronto.ca
Department of Physical and
Environmental Sciences,
University of Toronto
Scarborough,
Toronto, Ontario M1C 1A4,
Canada

B. Kierdaszuk
borys@biogeo.uw.edu.pl
Department of Biophysics,
Institute of Experimental Physics,
Faculty of Physics,
University of Warsaw, 02-089,
Warsaw, Poland

Bahareh Honarparvar
Honarparvar@ukzn.ac.za

School of Pharmacy and
Pharmacology,
University of KwaZulu-Natal,
Durban, 4001, South Africa

Bin Dong
dong@dlnu.edu.cn
School of Physics and Materials
Engineering,
Dalian Nationalities University,
Dalian, China

Boaz G. Oliveira
boazgaldino@gmail.com
Instituto de Ciências Ambientais e
Desenvolvimento Sustentável,
Universidade Federal da Bahia,
47801-100, Barreiras, Brazil

Burak Erman
berman@ku.edu.tr
Department of Chemical and
Biological Engineering,
Koc University, Istanbul, Turkey

Carles Curutchet
carles.curutchet@ub.edu
Departament de Físicoquímica,
Facultat de Farmàcia, Universitat
de Barcelona,
Av. Joan XXIII s/n, 08028
Barcelona, Spain

Chihai Yang
chihai.yang@molecular-
networks.com
Molecular Networks GmbH,
91052 Erlangen, Germany

Christian Kramer
Christian.Kramer@roche.com
Department of Theoretical
Chemistry,
Faculty for Chemistry and
Pharmacy,
Center for Molecular Biosciences
Innsbruck (CMBI),
Leopold-Franzens University
Innsbruck,
Innrain 80/82, A-6020
Innsbruck, Austria

Clifford E. Woodward
c.woodward@adfa.edu.au
School of Physical, Environmental
and Mathematical Sciences,
University of New South Wales,
Canberra ACT 2600, Australia

Daniel A. Keedy
d@nielkeedy.com
Department of Bioengineering and
Therapeutic Sciences and

California Institute for Quantitative
Biology,
University of California, San
Francisco,
San Francisco, CA, USA

David E. Shaw
David.Shaw@DEShawResearch.com
D. E. Shaw Research,
New York, New York

David L. Mobley
dmobley@mobleyleab.org
Department of Pharmaceutical
Sciences and Department of
Chemistry,
University of California, Irvine,
147 Bison Modular, Irvine, CA,
92697, USA

David T. Jones and Domenico
Cozzetto
d.t.jones@ucl.ac.uk
Bioinformatics Group, Department
of Computer Science,
University College London,
Gower Street, London WC1E 6BT,
UK

Debashis Mukherjee
pcdemu@gmail.com
Raman Centre for Atomic,
Molecular and Optical Sciences,
Indian Association for the
Cultivation of Sciences,
Jadavpur, Kolkata, India.

Denis C. Shields
denis.shields@ucd.ie
School of Medicine and Medical
Science,
University College Dublin,
Dublin 4, Ireland

Dick B. Janssen
d.b.janssen@rug.nl
Biotransformation and
Biocatalysis,
Groningen Biomolecular Sciences
and Biotechnology Institute,
University of Groningen,
Groningen,
The Netherlands

Donald Hamelberg
dhamelberg@gsu.edu
Department of Chemistry and the
Center for Biotechnology and Drug
Design,
Georgia State University, Atlanta,
Georgia 30302-3965, United States

Edward C. Stites estites@path.wustl.edu Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, Missouri	University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom	Hans Peter Lüthi hans.luethi@phys.chem.ethz.ch ETH Zurich, Laboratorium für Physikalische Chemie, Zurich, Switzerland	Laboratory of Molecular Biophysics, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, United States
Edward S. Chen eschen@bcm.edu Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030, USA	Frank M. Boeckler frank.boeckler@uni-tuebingen.de Laboratory for Molecular Design and Pharmaceutical Biophysics, Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany	Harold A. Scheraga has5@cornell.edu Baker Laboratory of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14850-1301, United States	Jean-François Halet halet@univ-rennes1.fr Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS, Université de Rennes 1, 35042, Rennes Cédex, France
Elsa Sanchez-Garcia esanchez@mpi-muelheim.mpg.de Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany	G. Tiana guido.tiana@unimi.it Department of Physics, Università degli Studi di Milano, via Celoria 16, 20133 Milano, Italy	Helena M. Petrilli hmpetrilli@if.usp.br Instituto de Física, Universidade de São Paulo, Rua do Matão Travessa R, Nr.187, Cidade Universitária, CP 66318, 05508-090, São Paulo, Brazil	Jens Carlsson jens.carlsson@dbb.su.se Science for Life Laboratory, Stockholm University, Box 1031, SE-171 21 Solna, Sweden
Emppu Salonen emppu.salonen@aalto.fi Department of Applied Physics, Aalto University, Finland	Gajendra P. S. Raghava raghava@imtech.res.in G. P. S. Raghava, Scientist & Head Bioinformatics Centre, CSIR-Institute of Microbial Technology, Sector-39A, Chandigarh, India	Hossein Fazli fazli@iasbs.ac.ir Department of Physics, Institute for Advanced Studies in Basic Sciences (IASBS), 45137-66731, Zanjan, Iran	Jesús A. Izaguirre izaguirr@nd.edu Graduate Program in Bioengineering, University of Notre Dame, Notre Dame, Indiana
Enrique Sánchez Marcos sanchez@us.es Department of Physical Chemistry, University of Seville, 41012 Seville, Seville, Spain	George Khelashvili gek2009@med.cornell.edu Department of Physiology and Biophysics, Weill Cornell Medical College of Cornell University, New York, New York	Hugh I. Kim hughkim@postech.edu Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang 790-784, Republic of Korea	Jesús Sánchez-Márquez jesus.sanchezmarquez@uca.es Departamento de Química-Física, Facultad de Ciencias, Universidad de Cádiz, Campus Universitario Río San Pedro, 11510, Puerto Real, Cádiz, Spain
Ernest Fraenkel fraenkel-admin@mit.edu Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA	Giovanni Grazioso giovanni.grazioso@unimi.it Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Farmaceutica "Pietro Pratesi", Università degli Studi di Milano, Via L. Mangiagalli 25, 20133, Milan, Italy	Ilya A. Vakser vakser@ku.edu Center for Bioinformatics, The University of Kansas, Lawrence, Kansas	Jianying Zhang, Xuedong Gong nanjinger@163.com College of Material and Chemical Engineering, ChuZhou University, ChuZhou, 239000, Anhui, China
Ernst-Walter Knapp knapp@chemie.fu-berlin.de Department of Biology, University of Science, Pyongyang, DPR Korea	Giulio Rastelli giulio.rastelli@unimore.it Life Sciences Department, University of Modena and Reggio Emilia, Via Campi 183, 41125 Modena, Italy	Ion I. Măndoiu ion@enr.uconn.edu Computer Science and Engineering Department, University of Connecticut, Storrs, Connecticut 06269, United States	Jim Pfaendtner jpfpaendt@uw.edu Department of Chemical Engineering, University of Washington, Seattle, Washington
Fabio Sterpone fabio.sterpone@ibpc.fr Laboratoire de Biochimie Théorique, IBPC, CNRS UPR9080, Univ. Paris Diderot, Sorbonne Paris Cité, 13 rue Pierre et Marie Curie, 75005 Paris, France	Guang Song gsong@iastate.edu Department of Computer Science, Iowa State University, Ames, Iowa	Jakob Wohler jacke@kth.se Department of Forest Products Technology, Aalto University, P.O. Box 16300, FI-00076 Espoo, Finland	Jin-ku Bao baojinku@scu.edu.cn School of Life Sciences and Key Laboratory of Bio-resources, Ministry of Education, & State Key Laboratory of Biotherapy, Sichuan University, Chengdu, 610064, China
Federico Fogolari federico.fogolari@uniud.it Dipartimento di Scienze Mediche e Biologiche, Università di Udine, Piazzale Kolbe, Udine, Italy	Guglielmo Monaco gmonaco@unisa.it Department of Chemistry and Biology, University of Salerno, Fisciano, Italy	Jaroslav Koča jkoca@chemi.muni.cz Central European Institute of Technology (CEITEC), Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic	Jingping Zhang jpzhang@nenu.edu.cn Department of Chemistry, Northeast Normal University, Changchun, China
Francesco L. Gervasio f.l.gervasio@ucl.ac.uk Department of Chemistry and Institute of Structural and Molecular Biology,		Jay R. Knutson knutsonj@helix.nih.gov Optical Spectroscopy Section,	

- Jiří Vondrášek
jiri.vondrasek@uochb.cas.cz
Institute of Organic Chemistry and Biochemistry,
Flemingovonáměstí 2, Prague 6,
160 10, Czech Republic
- Jitao T. Huang
jthuang@nankai.edu.cn
Department of Chemistry and National Laboratory of Elemento-Organic Chemistry,
Nankai University, Tianjin, People's Republic of China
- Joan-Emma Shea
shea@chem.ucsb.edu
Department of Chemistry and Biochemistry,
University of California at Santa Barbara,
Santa Barbara,
California 93106, United States
- Jógvan Magnus Haugaard Olsen
magnus.olsen@epfl.ch
Laboratory of Computational Chemistry and Biochemistry,
École Polytechnique Fédérale de Lausanne (EPFL),
CH-1015 Lausanne, Switzerland
- Jonathan C. Fuller
jonathan.fuller@h-its.org
Molecular and Cellular Modeling Group,
Heidelberg Institute for Theoretical Studies (HITS),
69118 Heidelberg
- Juan Andrés
andres@uji.es
Departament de Química Física i Analítica,
Universitat Jaume I, 12071,
Castellón, Spain
- Juan Fernández-Recio
juanf@bsc.es
Joint BSC-IRB Research Program in Computational Biology,
Life Science Department,
Barcelona Supercomputing Center, Barcelona, Spain
- Kamila Réblová
kristina@physics.muni.cz
Central European Institute of Technology (CEITEC),
Masaryk University, Kamenice 5,
625 00, Brno, Czech Republic
- Kiatwatee Choowongkamon
fsciktc@ku.ac.th
Department of Biochemistry, Faculty of Science, Kasetsart University,
Chatuchak, Bangkok 10900, Thailand.
- Kumar Vanka
k.vanka@ncl.res.in
Physical Chemistry Division,
National Chemical Laboratory,
Pune, Maharashtra, India
- L. Alisaraie
laleh.alisaraie@mun.ca
L. Alisaraie, School of Pharmacy, Memorial University of Newfoundland,
300 Prince Philip Dr, St. John's, Newfoundland, A1B 3V6, Canada.
- Lauren E. Marbella
lem64@pitt.edu
Department of Chemistry, University of Pittsburgh,
Pittsburgh,
Pennsylvania 15260, United States
- Letif Mones
lam81@cam.ac.uk
Engineering Department, University of Cambridge,
Cambridge, United Kingdom
- Liang Bian
bianliang@ms.xjb.ac.cn
Xinjiang Key Laboratory of Electronic Information Materials and Devices,
CAS, Urumqi, 830011,
Xinjiang, China
- Liao Y. Chen
Liao.Chen@utsa.edu
Department of Physics, University of Texas at San Antonio,
One UTSA Circle, San Antonio, Texas 78249, United States
- Lluís Blancafort
lluis.blancafort@udg.edu
Institut de Química Computacional i Catàlisi and Departament de Química,
Universitat de Girona,
Campus de Montilivi, 17071 Girona, Spain
- Lorna J. Smith
lorna.smith@chem.ox.ac.uk
Department of Chemistry, Inorganic Chemistry Laboratory, University of Oxford,
South Parks Road, Oxford, OX1 3QR, UK
- Macoto Kikuchi
kikuchi@cmc.osaka-u.ac.jp
Cybermedia Center,
Osaka University, Toyonaka, Japan
- Marco Mor
marco.mor@unipr.it
Dipartimento di Farmacia,
- Università degli Studi di Parma, Viale delle Scienze 27/A,
I-43124, Parma, Italy
- Marian Verdes
marian.verdes@uam.es
Departamento de Química Física Aplicada,
Facultad de Ciencias, C-14,
Universidad Autónoma de Madrid, Cantoblanco, 28049, Madrid, Spain
- Mariana Kozłowska
mari.kozłowska@gmail.com
Institute of Chemistry, University of Białystok,
Hurtowa 1, 15-399, Białystok, Poland
- Mario Stanke
mario.stanke@uni-greifswald.de
Institute of Mathematics and Computer Science,
University of Greifswald,
Greifswald, Germany
- Mark S. Gordon
mark@si.msg.chem.iastate.edu
Department of Chemistry and Ames Laboratory,
Iowa State University,
Ames, Iowa, United States
- Mark S.P. Sansom
mark.sansom@bioch.ox.ac.uk
Department of Biochemistry, University of Oxford, Oxford,
United Kingdom
- Markus A. Lill
mlill@purdue.edu
Department of Medicinal Chemistry and Molecular Pharmacology,
College of Pharmacy, Purdue University,
West Lafayette, Indiana
- Markus Zweckstetter
mzwecks@gwdg.de
Department of NMR-Based Structural Biology,
Max Planck Institute for Biophysical Chemistry,
37077 Göttingen, Germany
- Mehdi D. Esrafil
esrafil@maragheh.ac.ir
Laboratory of Theoretical Chemistry,
Department of Chemistry, University of Maragheh,
Maragheh, Iran
- Michael Feig
feig@msu.edu
Department of Biochemistry & Molecular Biology,
- Michigan State University, 603 Wilson Road,
BCH 218, East Lansing, MI 48824, United States.
- Michael T. Bowers
bowers@chem.ucsb.edu
Department of Chemistry and Biochemistry,
University of California, Santa Barbara,
California 93106, United States
- Minh N. Nguyen
minhn@bii.a-star.edu.sg
Biomolecular Modeling and Design Division,
Singapore 138671 Singapore
- Minh Tho Nguyen
minh.nguyen@chem.kuleuven.be
Institute for Computational Science and Technology (ICST),
Quang Trung Software City,
Ho Chi Minh City, Vietnam
- Minori Abe
minoria@tmu.ac.jp
Department of Chemistry, Graduate School of Science and Engineering,
Tokyo Metropolitan University, Hachioji,
Tokyo, Japan
- Mohsen Shahlaei
mohsenshahlaei@yahoo.com
Medicinal Chemistry department, Faculty of Pharmacy,
Kermanshah University of Medical Sciences,
Kermanshah, Iran
- N. Latha
lata@bic-svc.ac.in
Bioinformatics Infrastructure Facility,
Sri Venkateswara College (University of Delhi),
Dhaura Kuan, New Delhi, India
- Nagarajan Vaidehi
NVaidehi@coh.org
Division of Immunology, Beckman Research Institute of the City of Hope,
1500 East Duarte Road, Duarte, California 91010, United States
- Nematollah Arshadi
narshadi@email.com
Department of Chemistry, Faculty of Sciences,
University of Zanjan, Zanjan, Iran
- Oana Cramariuc
oana.cramariuc@tut.fi
Department of Physics,

Tampere University of
Technology,
Tampere, Finland

Olga V. Kalinina
kalinina@mpi-inf.mpg.de
Department for Computational
Biology and Applied Algorithmics,
Max Planck Institute for
Informatics,
Campus E1 4, 66123 Saarbrücken,
Germany

Oscar Olvera-Neria
oon@correo.azc.uam.mx
Área de Física Atómica Molecular
Aplicada (FAMA), CBI,
Universidad
Autónoma Metropolitana-
Azcapotzalco,
Av. San Pablo 180,
Col. Reynosa Tamaulipas,
Mexico, D. F., 02200, Mexico

Paul M. Zimmerman
paulzim@umich.edu
Department of Chemistry,
University of Michigan,
Ann Arbor, Michigan

Pavel Banáš
pavel.banas@upol.cz
Regional Centre of Advanced
Technologies and Materials,
Department of Physical Chemistry,
Faculty of Science,
Palacky University, tr. 17 listopadu
12,
771 46 Olomouc, Czech Republic

Pavel Jungwirth
pavel.jungwirth@uochb.cas.cz
Department of Physics,
Tampere University of
Technology,
P.O. Box 692, FI-33101 Tampere,
Finland

Petr Bouř
bour@uochb.cas.cz
Group of Molecular Spectroscopy,
Institute of Organic Chemistry and
Biochemistry,
Academy of Sciences, Prague,
Czech Republic

Pinak Chakrabarti
pinak@jcbose.ac.in
Department of Biochemistry,
Bose Institute, Kolkata,
West Bengal, India

Piotr Cysewski
piotr.cysewski@cm.umk.pl
Department of Physical Chemistry,
Collegium Medicum of Bydgoszcz,
Nicolaus Copernicus University in
Toruń,

Kurpińskiego 5, 85-950,
Bydgoszcz, Poland

Pompozhi Protasis Thankachan
thankachan1950@gmail.com
Department of Chemistry,
Indian Institute of Technology
Roorkee,
Roorkee, 247 667, India

Pradeep Kumar Naik
pknaik1973@gmail.com
Department of Biotechnology and
Bioinformatics,
Jaypee University of Information
Technology,
Waknaghat, Solan, Himachal
Pradesh, India

Prashant Nagpal
pnagpal@colorado.edu
Department of Chemical and
Biological Engineering,
University of Colorado, Boulder,
Colorado, 80309, United States

Przemysław Czeleń, Beata Szeffler
przemekcz@cm.umk.pl
Department of Physical Chemistry,
Collegium Medicum,
Nicolaus Copernicus University,
Kurpińskiego 5, 85-950,
Bydgoszcz, Poland

Pu Tian
tianpu@jlu.edu.cn
School of Life Sciences,
Jilin University,
Changchun, China

R. R. Netz
rnetz@physik.fu-berlin.de
Fachbereich Physik,
Freie Universität Berlin,
14195 Berlin, Germany

Rainer A. Böckmann
rainer.boeckmann@fau.de
Computational Biology,
Department of Biology,
University of Erlangen-Nürnberg,
Staudtstr. 5, 91052 Erlangen,
Germany

Ralph Jimenez
rjimenez@jila.colorado.edu
Department of Chemistry and
Biochemistry,
University of Colorado at Boulder,
215 UCB, Boulder,
Colorado 80309, United States

Ramesh Chandra Deka
ramesh@tezu.ernet.in
Department of Chemical Sciences,
Tezpur University, Tezpur,
Napaam,
Assam, 784028, India

Randy J. Zauhar
r.zauhar@uscience.edu
Department of Chemistry and
Biochemistry,
University of the Sciences,
600 S. 43rd Street, Philadelphia,
PA, 19104, USA

Renxiao Wang
wangrx@mail.sioc.ac.cn
State Key Laboratory of
Bioorganic and Natural Products
Chemistry,
Collaborative Innovation Center of
Chemistry for Life Sciences,
Shanghai Institute of Organic
Chemistry,
Chinese Academy of Sciences,
Shanghai,
People's Republic of China

Robert B. Best
robertbe@helix.nih.gov
Laboratory of Chemical Physics,
National Institute of Diabetes and
Digestive and
Kidney Diseases, National Institutes
of Health,
Bethesda, Maryland 20892-0520,
United States

Roberto Salcedo
salcedo@unam.mx
Instituto de
Investigaciones en Materiales,
Universidad Nacional Autónoma
de México,
Avenida Universidad 3000,
Mexico, D.F., 04510, Mexico

Ronen Zangi
r.zangi@ikerbasque.org
Department of Organic Chemistry
I,
University of the Basque Country
UPV/EHU,
Avenida de Tolosa 72,
20018 San Sebastian, Guipúzcoa,
Spain

S. J. Marrink
s.j.marrink@rug.nl
Groningen Biomolecular Sciences
and Biotechnology Institute,
Zernike Institute for Advanced
Materials,
University of Groningen,
Nijenborgh 7,
9747 AG Groningen, Groningen,
The Netherlands

S. Joshua Swamidass
swamidass@wustl.edu
Division of Biology and Biological
Sciences,
Washington University School of
Medicine,
St. Louis, MO 63130, US

Sandro C. Izidoro
sandroizidoro@unifei.edu.br
Advanced Campus at Itabira,
Universidade Federal de Itajubá,
Itajubá, MG 35903-087, Brazil

Sebastian Höfener
sebastian.hoefener2@kit.edu
Institut für Physikalische Chemie,
Fakultät für Chemie und
Biowissenschaften,
Karlsruher Institut für Technologie
(KIT),
Karlsruhe, Germany

Shang-Te Danny Hsu
sthsu@gate.sinica.edu.tw
Institute of Biological Chemistry,
Academia Sinica, 128, Section 2,
Academia Road, Taipei 11529,
Taiwan

Sharmila Anishetty
sharmi.anishetty@gmail.com
Center for Biotechnology,
Anna University, Chennai,
600 025, India

Simone Fulle
fulle@bio.mx
BioMed X Innovation Center,
Im Neuenheimer Feld 583,
69120 Heidelberg, Germany

Simone Morpurgo
simone.morpurgo@uniroma1.it
Dipartimento di Chimica,
Università degli Studi di Roma "La
Sapienza,"
Roma, Italia

Sol M. Mejía
sol.mejia@javeriana.edu.co
Grupo de Investigación Fitoquímica
Universidad Javeriana (GIFUJ),
Departamento de Química,
Facultad de Ciencias,
Pontificia Universidad Javeriana,
Carrera 7 No. 40-62, Bogotá, D.
C., Colombia

Souvik Maiti
souvik@igib.res.in
Academy of Scientific and
Innovative Research (AcSIR),
Anusandhan Bhawan,
2 Rafi Marg, New Delhi 110001,
India

Stephanie N. Lewis
Genetics, Bioinformatics, and
Computational Biology Program,
Virginia Tech, Blacksburg, VA,
USA

Suzana K. Straus
sstraus@chem.ubc.ca
Suzana K. Straus, Chemistry
Department,

University of British Columbia,
2036 Main Mall, Vancouver,
BC V6T 1Z1, Canada

Tamsyn A. Hilder
tamsyn.hilder@anu.edu.au
Computational Biophysics Group,
Research School of Biology,
Australian National University,
Canberra,
ACT 0200, Australia

Tetsuya Sato and Mikita Suyama
mikita@bioreg.kyushu-u.ac.jp
CREST, Japan Science and
Technology Agency,
812-8582 Fukuoka, Japan

Tian Tang, Subir Bhattacharjee
tian.tang@ualberta.ca
Water Planet Engineering, 721D,
South Glasgow Avenue,
Inglewood,
CA 90301, United States

Umesh Yadava
u_yadava@yahoo.com
Department of Physics,
D.D.U. Gorakhpur University,
Gorakhpur, 273009, India

V. V. Andrushchenko
andrushchenko@uochb.cas.cz
Institute of Organic Chemistry and
Biochemistry,
Academy of Sciences, Flemingovo
náměstí 2,
16610, Prague, Czech Republic

Vasile Chiş
vasile.chis@phys.ubbcluj.ro
Faculty of Physics,
Babeş-Bolyai University,
1 Kogălniceanu, 400084,
Cluj-Napoca, Romania

Victor M. Rosas-García
victor.rosasgr@uanl.edu.mx
Facultad de Ciencias Químicas,
Universidad Autónoma de Nuevo
León,
UANL, Ave. Universidad S/N,
Ciudad Universitaria,
San Nicolás de los Garza,
N. L., Mexico, C. P. 66451

Viktor Pilepić
vpilepic@pharma.hr
Faculty of Pharmacy and
Biochemistry,
University of Zagreb,
A. Kovačića 1, Zagreb, Croatia

Vincent Tognetti
vincent.tognetti@univ-rouen.fr
Normandy University,
COBRA UMR 6014 & FR 3038,
Université de Rouen, INSA Rouen,

CNRS, Mont St Aignan, Cedex,
France

Vladimir Sobolev
vladimir.sobolev@weizmann.ac.il
Department of Plant and
Environmental Sciences,
Weizmann Institute of Science,
Rehovot, Israel

Wei Han Tu
tuweiha@gmail.com
Anderson Junior College,
4500 Ang Mo Kio Avenue 6,
Singapore,
569843, Singapore

Wenzhen Lai
wenzhenlai@ruc.edu.cn.
Department of Chemistry,
Renmin University of China,
Beijing, 100872, China

Wenzuo Li
liwenzuo2004@126.com
The Laboratory of Theoretical and
Computational Chemistry,
College of Chemistry and
Chemical Engineering
Yantai University, Yantai, 264005,
People's Republic of China

Wenzuo Li
liwenzuo2004@126.com
The Laboratory of Theoretical and
Computational Chemistry,
School of Chemistry and Chemical
Engineering,
Yantai University, Yantai, 264005,
People's Republic of China

Wiktor Zierkiewicz
Wiktor.Zierkiewicz@pwr.edu.pl
Department of Chemistry,
Wrocław University of
Technology,
Wrocław, Poland

William A. Goddard III
wag@wag.caltech.edu
Materials and Process Simulation
Center (MC-139-74),
California Institute of Technology,
Pasadena, California 91125, United
States

Xiang-Qun Xie
xix15@pitt.edu
3501 Terrace Street, 529 Salk Hall,
University of Pittsburgh,
Pittsburgh, PA 15261, U.S.A

Yan Li
yanli@pku.edu.cn
Key Laboratory for the Physics and
Chemistry of Nanodevices,
BNLMS,
College of Chemistry and
Molecular Engineering,

Peking University, Beijing, China

Yanru Huang
huangganen12@sina.cn
College of Science,
Liaoning Shihua University,
Fushun, 113001, China

Yasuteru Shigeta
shigeta@ccs.tsukuba.ac.jp
Division of Life Science,
Center for Computational Sciences,
University of Tsukuba, Ibaraki,
Japan

Yellamraju U. Sasidhar
sasidhar@chem.iitb.ac.in
Department of Chemistry,
Indian Institute of Technology
Bombay,
Powai, Mumbai, 400076, India

Yi Ren and Kai-Chung Lau
renyi@scu.edu.cn
College of Chemistry and Key
State Laboratory of Biotherapy,
Sichuan University,
Chengdu, China

Yong-Qing Qiu
qiuyq466@nenu.edu.cn
Institute of Functional Material
Chemistry,
Faculty of Chemistry,
Northeast Normal University,
Changchun,
Jilin, 130024, People's Republic of
China

Yuanbin She
sheyb@bjut.edu.cn
State Key Laboratory Breeding
Base of Green Chemistry-Synthesis
Technology,
College of Chemical Engineering,
Zhejiang University of
Technology,
Hangzhou, 310014, China

Yuguang Mu
ygmu@ntu.edu.sg
School of Biological Sciences,
Nanyang Technological University,
Singapore 637551, Singapore

Yuki Naito
y-naito@dbcls.rois.ac.jp
Database Center for Life Science
(DBCLS),
Research Organization of
Information and Systems,
1111 Yata, Mishima, Shizuoka
411-8540, Japan

Yun-Dong Wu
wuyd@pkusz.edu.cn
Laboratory of Computational
Chemistry and Drug Design,
Laboratory of Chemical Genomics,

Peking University Shenzhen
Graduate School,
Shenzhen, 518055, China

Zhenggang Lan
lanzg@qibebt.ac.cn
Key Laboratory of Biobased
Materials,
Qingdao Institute of Bioenergy and
Bioprocess Technology,
Chinese Academy of Sciences,
Qingdao,
266101 Shandong, People's
Republic of China

Zhijun Li
z.li@uscience.edu
Department of Chemistry &
Biochemistry,
University of the Sciences in
Philadelphia,
Box 48, Philadelphia, PA, 19104,
USA

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Editor:

R.Mutyala.
MMCC Results

RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.

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Assistant Editors:

Anston Feenstra, Vrije Univ., Amsterdam, Netherlands

Naresh Aerra, Rational Labs, Hyderabad, India.

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Water Dispersion Interactions Strongly Influence Simulated Structural Properties of Disordered Protein States

Stefano Piana, Alexander G. Donchev, Paul Robustelli, and David E. Shaw [D. E. Shaw Research, New York]

J. Phys. Chem. B., **119**, 5113–5123, 2015.

Many proteins can be partially or completely disordered under physiological conditions. Structural characterization of these disordered states using experimental methods can be challenging, since they are composed of a structurally heterogeneous ensemble of conformations rather than a single dominant conformation. We find that the water models typically used in MD simulations significantly underestimate London dispersion interactions, and speculate that this may be a possible reason for these erroneous results. To test this hypothesis, we create a new water model, TIP4P-D, that approximately corrects for these deficiencies in modeling water dispersion interactions while maintaining compatibility with existing physics-based models.



MMCC Results

8013 Los Sabalos Street
San Diego, CA 92126
Tel. (858) 663-0162
e-mail: mmccresults@gmail.com

Dr. R. Mutyala.
RR Labs Inc., 8013 Los Sabalos St.
San Diego, CA 92126

**Editors Emeritus: Bruce Gelin, Ph.D.
David Busath, M.D.**

*Dr. Gelin was founder of MMCC Results and edited volumes 1-6.
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Assistant Editors:

Sowmya .N
Rational Labs, Hyderabad., India

Sambasivareddy M
RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design

drexplorer: A tool to explore dose–response relationships and drug–drug interactions

Pan Tong, Kevin R. Coombes, Faye M. Johnson, Lauren A. Byers, Lixia Diao, Diane D. Liu, J. Jack Lee, John V. Heymach, and Jing Wang [Departments of Bioinformatics and Computational Biology, Houston]

Bioinformatics, **31**, 1692-1694, 2015.

Nonlinear dose–response models are primary tools for estimating the potency [e.g. half-maximum inhibitory concentration (IC) known as IC₅₀] of anti-cancer drugs. We present *drexplorer* software, which enables biologists to evaluate replicate reproducibility, detect outlier data points, fit different models, select the best model, estimate IC values at different percentiles and assess drug–drug interactions. The *drexplorer* R package is freely available from GitHub at <https://github.com/nickytong/drexplorer>. A graphical user interface is shipped with the package.

Diarylsulfonamides and their bioisosteres as dual inhibitors of alkaline phosphatase and carbonic anhydrase: Structure activity relationship and molecular modelling studies

Mariya al-Rashida, Syeda Abida Ejaz, Sharafat Ali, Aisha Shaukat, Mehwish Hamayoun, Maqsood Ahmed, Jamshed Iqbal [COMSATS Institute of Information Technology, Abbottabad]

Bioorg. and Med.Chem., **23**, 2435-2444, 2015.

The effect of bioisosteric replacement of carboxamide linking group with sulfonamide linking group, on alkaline phosphatase (AP) and carbonic anhydrase (CA) inhibition activity of aromatic benzenesulfonamides was investigated. A series of carboxamide linked aromatic benzenesulfonamides **1a–1c**, **2a–2d** and their sulfonamide linked bioisosteres **3a–3d**, **4a–4d** was synthesized and evaluated for inhibitory activity against bovine tissue non-specific alkaline phosphatase (TNAP), intestinal alkaline phosphatase (IAP) and bCA II. A significant increase in CA inhibition activity was observed upon bioisosteric replacement of carboxamide linking group with a sulfonamide group.

Hotspots in an Obligate Homodimeric Anticancer Target. Structural and Functional Effects of Interfacial Mutations in Human Thymidylate Synthase

Outi M. H. Salo-Ahen, Anna Tochowicz, Cecilia Pozzi, Daniela Cardinale, Stefania Ferrari, Yap Boum, Stefano Mangani, Robert M. Stroud, Puneet Saxena, Hannu Myllykallio, Maria Paola Costi, Glauco Ponterini, and Rebecca C. Wade [Heidelberg Institute for Theoretical Studies]

J.Med.Chem., **58**, 3572–3581, 2015.

Human thymidylate synthase (hTS), a target for antiproliferative drugs, is an obligate homodimer. Single-point mutations to alanine at the monomer–monomer interface may enable the identification of specific residues that delineate sites for drugs aimed at perturbing the protein–protein interactions critical for activity. We computationally identified putative hotspot residues at the interface and designed mutants to perturb the intersubunit interaction. Dimer dissociation constants measured by a FRET-based assay range from 60 nM for wild-type hTS up to about 1 mM for single-point mutants and agree with computational predictions of the effects of these mutations.

Peptide Triazole Inactivators of HIV-1 Utilize a Conserved Two-Cavity Binding Site at the Junction of the Inner and Outer Domains of Env gp120

Rachna Aneja, Adel A. Rashad, Huiyuan Li, Ramalingam Venkat Kalyana Sundaram, Caitlin Duffy, Lauren D. Bailey, and Irwin Chaiken [Drexel University College of Medicine]

J.Med.Chem., **58**, 3843–3858, 2015.

We used coordinated mutagenesis, synthetic design, and flexible docking to investigate the structural mechanism of Env gp120 encounter by peptide triazole (PT) inactivators of HIV-1. Prior results demonstrated that the PT class of inhibitors suppresses binding at both CD4 and coreceptor sites on Env and triggers gp120 shedding, leading to cell-independent irreversible virus inactivation. Despite these enticing anti-HIV-1 phenotypes, structural understanding of the PT–gp120 binding mechanism has been incomplete. Here we found that PT engages two inhibitor ring moieties at the junction between the inner and outer domains of the gp120 protein.

Medicinal Chemistry and Drug Design (Cont'd)

pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures

Douglas E. V. Pires, Tom L. Blundell, and David B. Ascher
[University of Cambridge]

J.Med.Chem., **58**, 4066–4072, 2015.

Drug development has a high attrition rate, with poor pharmacokinetic and safety properties a significant hurdle. Computational approaches may help minimize these risks. We have developed a novel approach (pkCSM) which uses graph-based signatures to develop predictive models of central ADMET properties for drug development. pkCSM performs as well or better than current methods. A freely accessible web server, which retains no information submitted to it, provides an integrated platform to rapidly evaluate pharmacokinetic and toxicity properties.

Molecular docking study of macrocycles as Fk506-binding protein inhibitors

Corey A. MacDonald, Russell J. Boyd [Dalhousie University]

J. Mol.Graph. and Mod., **59**, 117-122, 2015.

To prepare for future resistance, new methods are being explored for novel treatment of malaria. The current work uses high performance docking methods to model different substrates binding into the active sites of varying Homo sapien and Plasmodium peptidyl-prolyl cis/trans isomerase enzymes and compares their subsequent docking scores. This approach has shown that the substrates ILS-920 and WYE-592 will bind less-favourably with hFKBP12 and PfFKBP35 compared to a competing substrate rapamycin; however, the binding appears to be more favourable in PvFKBP35.

Dynamics Based Pharmacophore Models for Screening Potential Inhibitors of Mycobacterial Cyclopropane Synthase

Chinmayee Choudhury, U. Deva Priyakumar, and G. Narahari Sastry [Indian Institute of Chemical Technology, Hyderabad]

J.Chem. Infor. and Mod. **55**, 848–860, 2015.

The therapeutic challenges in the treatment of tuberculosis demand multidisciplinary approaches for the identification of potential drug targets as well as fast and accurate techniques to screen huge chemical libraries. Mycobacterial cyclopropane synthase (CmaA1) has been shown to be essential for the survival of the bacteria due to its critical role in the synthesis of mycolic acids. The present study proposes pharmacophore models based on the structure of CmaA1 taking into account its various states in the cyclopropanation process, and their dynamic nature as assessed using molecular dynamics (MD) simulations.

Quantitative Structure-Activity Relations

Discovery of potent and selective urea-based ROCK inhibitors: Exploring the inhibitor's potency and ROCK2/PKA selectivity by 3D-QSAR, molecular docking and molecular dynamics simulations

Ding Mei, Yan Yin, Fanhong Wu, Jiaying Cui, Hong Zhou, Guofeng Sun, Yu Jiang, Yangbo Feng [The Scripps Research Institute, Florida]

Bioorg. and Med.Chem., **23**, 2505-2517, 2015.

An activity model and a selectivity model from 3D-QSAR studies were established by CoMFA and CoMSIA to explore the SAR. Then docking was used to study the binding modes between ligand and kinases (ROCK2 and PKA), and the molecular docking results were further validated by MD simulations. Computational results suggested that substitution containing positive charge attached to the middle phenyl ring, or electropositive group in urea linker was favored for both activity and ROCK2/PKA selectivity. Finally, three compounds were designed, and biological evaluation demonstrated that these molecular models were effective for guiding the design of potent and selective ROCK inhibitors.

Quantitative Structure-Activity Relations (Cont'd)

Aldose reductase inhibitors for diabetic complications: Receptor induced atom-based 3D-QSAR analysis, synthesis and biological evaluation

Bhawna Vyas [Punjabi University, Patiala], Manjinder Singh, Maninder Kaur, Malkeet Singh Bahia, Amteshwar Singh Jaggi, Om Silakari, Baldev Singh

J. Mol.Graph. and Mod., **59**, 59-71, 2015.

Herein, atom-based 3D-QSAR analysis was performed using receptor-guided alignment of 46 flavonoid inhibitors of aldose reductase (ALR2) enzyme. 3D-QSAR models were generated in PHASE programme, and the best model corresponding to PLS factor four (QSAR₄), was selected based on different statistical parameters (i.e. R^2_{train} , 0.96; Q^2_{test} , 0.81; SD, 0.26). The contour plots of different structural properties generated from the selected model were utilized for the designing of five new congener molecules.

1.2. Biopolymers

Bioinformatics and Cheminformatics

LocNES: a computational tool for locating classical NESs in CRM1 cargo proteins

Darui Xu, Kara Marquis, Jimin Pei, Szu-Chin Fu, Tolga Cağatay, Nick V. Grishin, and Yuh Min Chook [University of Texas Southwestern Medical Center at Dallas]

Bioinformatics. **31**, 1357-1365, 2015.

Classical nuclear export signals (NESs) are short cognate peptides that direct proteins out of the nucleus via the CRM1-mediated export pathway. CRM1 regulates the localization of hundreds of macromolecules involved in various cellular functions and diseases. We present a new NES predictor, LocNES. LocNES scans query proteins for NES consensus-fitting peptides and assigns these peptides probability scores using Support Vector Machine model, whose feature set includes amino acid sequence, disorder propensity, and the rank of position-specific scoring matrix score.

UProC: tools for ultra-fast protein domain classification

Peter Meinicke [University of Göttingen, Germany]

Bioinformatics. **31**, 1382-1388, 2015.

With rapidly increasing volumes of biological sequence data the functional analysis of new sequences in terms of similarities to known protein families challenges classical bioinformatics. The ultrafast protein classification (UProC) toolbox implements a novel algorithm ('Mosaic Matching') for large-scale sequence analysis. UProC is by three orders of magnitude faster than profile-based methods and in a metagenome simulation study achieved up to 80% higher sensitivity on unassembled 100 bp reads.

Bioinformatics and Cheminformatics (Cont'd)

GlycoMine: a machine learning-based approach for predicting N-, C- and O-linked glycosylation in the human proteome

Fuyi Li, Chen Li, Mingjun Wang, Geoffrey I. Webb, Yang Zhang, James C. Whisstock, and Jiangning Song [Monash University, Melbourne]

Bioinformatics. **31**, 1411-1419, 2015.

Glycosylation is a ubiquitous type of protein post-translational modification (PTM) in eukaryotic cells, which plays vital roles in various biological processes (BPs) such as cellular communication, ligand recognition and subcellular recognition. In this study, we present a novel bioinformatics tool called GlycoMine, which is a comprehensive tool for the systematic in silico identification of C-linked, N-linked, and O-linked glycosylation sites in the human proteome. GlycoMine was developed using the random forest algorithm and evaluated based on a well-prepared up-to-date benchmark dataset that encompasses all three types of glycosylation sites, which was curated from multiple public resources.

CONSRANK: a server for the analysis, comparison and ranking of docking models based on inter-residue contacts

Edrisse Chermak, Andrea Petta, Luigi Serra, Anna Vangone, Vittorio Scarano, Luigi Cavallo, and Romina Oliva [University "Parthenope" of Naples]

Bioinformatics. **31**, 1481-1483, 2015.

We present CONSRANK, a web tool for analyzing, comparing and ranking protein-protein and protein-nucleic acid docking models, based on the conservation of inter-residue contacts and its visualization in 2D and 3D interactive contact maps.

The anisotropic network model web server at 2015 (ANM 2.0)

Eran Eyal [Sheba Medical Center, 2 Sheba Rd], Gengkon Lum, and Ivet Bahar

Bioinformatics. **31**, 1487-1489, 2015.

The anisotropic network model (ANM) is one of the simplest yet powerful tools for exploring protein dynamics. Its main utility is to predict and visualize the collective motions of large complexes and assemblies near their equilibrium structures. The ANM server, introduced by us in 2006 helped making this tool more accessible to non-sophisticated users. We now provide a new version (ANM 2.0), which allows inclusion of nucleic acids and ligands in the network model and thus enables the investigation of the collective motions of protein-DNA/RNA and -ligand systems.

LS-VISM: A software package for analysis of biomolecular solvation

Shenggao Zhou [University of California, San Diego], Li-Tien Cheng, Hui Sun, Jianwei Che, Joachim Dzubiella, Bo Li and J. Andrew McCammon

J. Comp. Chem., **36**, 1047-1059, 2015.

We introduce a software package for the analysis of biomolecular solvation. The package collects computer codes that implement numerical methods for a variational implicit-solvent model (VISM). The input of the package includes the atomic data of biomolecules under consideration and the macroscopic parameters such as solute-solvent surface tension, bulk solvent density and ionic concentrations, and the dielectric coefficients. The output includes estimated solvation free energies and optimal macroscopic solute-solvent interfaces that are obtained by minimizing the VISM solvation free-energy functional among all possible solute-solvent interfaces enclosing the solute atoms.

Bioinformatics and Cheminformatics (Cont'd)

Peptide Triazole Inactivators of HIV-1 Utilize a Conserved Two-Cavity Binding Site at the Junction of the Inner and Outer Domains of Env gp120

Rachna Aneja, Adel A. Rashad, Huiyuan Li, Ramalingam Venkat Kalyana Sundaram, Caitlin Duffy, Lauren D. Bailey, and Irwin Chaiken [Drexel University College of Medicine]

J.Med.Chem., **58**, 3843–3858, 2015.

We used coordinated mutagenesis, synthetic design, and flexible docking to investigate the structural mechanism of Env gp120 encounter by peptide triazole (PT) inactivators of HIV-1. Prior results demonstrated that the PT class of inhibitors suppresses binding at both CD4 and coreceptor sites on Env and triggers gp120 shedding, leading to cell-independent irreversible virus inactivation. Despite these enticing anti-HIV-1 phenotypes, structural understanding of the PT–gp120 binding mechanism has been incomplete. Here we found that PT engages two inhibitor ring moieties at the junction between the inner and outer domains of the gp120 protein.

PockDrug: A Model for Predicting Pocket Druggability That Overcomes Pocket Estimation Uncertainties

Alexandre Borrel, Leslie Regad, Henri Xhaard, Michel Petitjean, and Anne-Claude Camproux [INSERM, UMRS-973]

J.Chem. Infor. and Mod. **55**, 882–895, 2015.

Predicting protein druggability is a key interest in the target identification phase of drug discovery. Here, we assess the pocket estimation methods' influence on druggability predictions by comparing statistical models constructed from pockets estimated using different pocket estimation methods: a proximity of either 4 or 5.5 Å to a cocrystallized ligand or DoGSite and fpocket estimation methods. We developed PockDrug, a robust pocket druggability model that copes with uncertainties in pocket boundaries. It is based on a linear discriminant analysis from a pool of 52 descriptors combined with a selection of the most stable and efficient models using different pocket estimation methods.

Protein Secondary Structure

NMR Analysis of Tuning Cross-Strand Phe/Tyr/Trp–Trp Interactions in Designed β -Hairpin Peptides: Terminal Switch from l to d Amino Acid as a Strategy for β -Hairpin Capping

Kamlesh M. Makwana and Radhakrishnan Mahalakshmi [Indian Institute of Science Education and Research]

J. Phys. Chem. B., **119**, 5376–5385, 2015.

Interaction among the side chains of aromatic amino acids is a well-known mechanism of protein and peptide structure stabilization, particularly in β sheets. Using short β -hairpin models bearing the sequence Ac-Leu-Xxx-Val-dPro-Gly-Leu-Trp-Val-NH₂, we report the surprising observation of significant destabilization in aryl–tryptophan interactions, which results in poorly folded peptide populations accompanied by lowering of stability. We find that such destabilization arises from forced occupancy of the indole ring in the shielded Edge position, in T-shaped aryl geometries.

Protein Side Chain Confirmation Prediction

The Impact of Side-Chain Packing on Protein Docking Refinement

Mohammad Moghadasi [Boston University, Boston], Hanieh Mirzaei, Artem Mamonov, Pirooz Vakili, Sandor Vajda, Ioannis Ch. Paschalidis, and Dima Kozakov

J.Chem. Infor. and Mod. **55**, 872–881, 2015.

We study the impact of optimizing the side-chain positions in the interface region between two proteins during the process of binding. Mathematically, the problem is similar to side-chain prediction, which has been extensively explored in the process of protein structure prediction. The protein–protein docking application, however, has a number of characteristics that necessitate different algorithmic and implementation choices. In this work, we implement a distributed approximate algorithm that can be implemented on multiprocessor architectures and enables a trade-off between accuracy and running speed.

Protein Confirmational Analysis

Protein alignment: Exact versus approximate. An illustration

Milan Randić [Laboratory of Chemometrics, Ljubljana] and Tomaž Pisanski

J. Comp. Chem., **36**, 1069–1074, 2015.

We illustrate solving the protein alignment problem exactly using the algorithm VESPA (very efficient search for protein alignment). We have compared our result with the approximate solution obtained with BLAST (basic local alignment search tool) software, which is currently the most widely used for searching for protein alignment. We have selected human and mouse proteins having around 170 amino acids for comparison. The exact solution has found 78 pairs of amino acids, to which one should add 17 individual amino acid alignments giving a total of 95 aligned amino acids.

Interactions between Bcl-xl and its inhibitors: Insights into ligand design from molecular dynamics simulation

Perna Priya, Atanu Maity, Sarmistha Majumdar, Shubhra Ghosh Dastidar [Bioinformatics Centre, Bose Institute]

J. Mol.Graph. and Mod., **59**, 1-13, 2015.

The Bcl-xl protein is a potential drug target for cancer, and it has a relatively flat and flexible binding pocket. ABT263 is one of the most promising molecules that inhibit Bcl-xl, and it was developed from its precursor ABT737 with suitable substitutions. However, the structural and mechanistic implications of those changes have not yet been reported. Molecular dynamics simulation has revealed that the conformational microstates of the complex of Bcl-xl and ABT263 shows heterogeneity at the binding interface with Bcl-xl in contrast to the precise interactions witnessed in case of ABT737.

Protein Conformational Analysis (Cont'd)

Conformational behavior of polyalanine peptides with and without protecting groups of varying chain lengths: population of PP-II structure!

Fateh S. Nandel [Panjab University, Chandigarh], Mohan L. Garg, Mohd Shafique

J. Mol.Mod., **21**, 123, 2015.

Oculopharyngeal muscular dystrophy (OPMD), a polyalanine myopathy, occurs due to expansion of homo-polyalanine stretch in normal polyadenylating binding protein nuclear 1 (PABPN1) protein from Ala₁₀ to Ala₁₁₋₁₇. Therefore, the conformational behavior of polyalanine peptides with n=10–17, with and without terminal protecting groups, have been investigated with different starting geometries in water by molecular dynamics simulation studies. Alanine peptides are shown to give rise to unordered structure irrespective of starting geometry and not more than two residues at a stretch have the same/similar set of ϕ , ψ values.

Molecular Simulation of Conformational Pre-Organization in Cyclic RGD Peptides

Amanda E. Wakefield, William M. Wuest, and Vincent A. Voelz [Temple University, Philadelphia]

J.Chem. Infor. and Mod. **55**, 806–813, 2015.

To test the ability of molecular simulations to accurately predict the solution-state conformational properties of peptidomimetics, we examined a test set of 18 cyclic RGD peptides selected from the literature, including the anticancer drug candidate cilengitide, whose favorable binding affinity to integrin has been ascribed to its pre-organization in solution. For each design, we performed all-atom replica-exchange molecular dynamics simulations over several microseconds and compared the results to extensive published NMR data. We find excellent agreement with experimental NOE distance restraints, suggesting that molecular simulation can be a useful tool for the computational design of pre-organized solution-state structure.

Protein Structure Analysis

Development of a coarse-grained α -chitin model on the basis of MARTINI forcefield

Zechuan Yu, Denvi Lau [City University of Hong Kong]

J. Mol.Mod., **21**, 128, 2015.

At nanoscale, atomistic simulation is widely used for investigating crystalline chitin fibers, the structural component for many biological materials. However, the longitudinal dimension of naturally occurring chitin fibers exceeds hundreds of nanometer, beyond the investigation range of all-atom simulation due to the limitation of computational power. Under this context, coarse-grained simulation is a useful alternative that facilitates the investigation of a large system. We develop a coarse-grained model for describing the structural and mechanical properties of α -chitin.

Protein Dynamics

All-Atom Internal Coordinate Mechanics (ICM) Force Field for Hexopyranoses and Glycoproteins

Yelena A. Arnautova, Ruben Abagyan, and Maxim Totrov [Molsoft L.L.C.]

J. Chem. Theor. and Comp., **11**, 2167–2186, 2015.

We present an extension of the all-atom internal-coordinate force field, ICMFF, that allows for simulation of heterogeneous systems including hexopyranose saccharides and glycan chains in addition to proteins. A library of standard glycan geometries containing α - and β -anomers of the most common hexapyranoses, i.e., d-galactose, d-glucose, d-mannose, d-xylose, l-fucose, N-acetylglucosamine, N-acetylgalactosamine, sialic, and glucuronic acids, is created based on the analysis of the saccharide structures reported in the Cambridge Structural Database.

Efficient Determination of Relative Entropy Using Combined Temperature and Hamiltonian Replica-Exchange Molecular Dynamics

Sunhwan Jo, Christophe Chipot, and Benoît Roux [University of Chicago, Chicago]

J. Chem. Theor. and Comp., **11**, 2234–2244, 2015.

The performance and accuracy of different simulation schemes for estimating the entropy inferred from free energy calculations are tested. The results obtained from replica-exchange molecular dynamics (REMD) simulations based on a simplified toy model are compared to exact numerically derived ones to assess accuracy and convergence. It is observed that the error in entropy estimation decreases by at least an order of magnitude and the quantities of interest converge much faster when the simulations are coupled via a temperature REMD algorithm and the trajectories from different temperatures are combined.

Early Stage P22 Viral Capsid Self-Assembly Mediated by Scaffolding Protein: Atom-Resolved Model and Molecular Dynamics Simulation

Jiajian Jiang, Jing Yang, Yuriy V. Sereda, and Peter J. Ortoleva [Department of Chemistry, Indiana University]

J. Phys. Chem. B., **119**, 5156–5162, 2015.

Molecular dynamics simulation of an atom-resolved bacteriophage P22 capsid model is used to delineate the underlying mechanism of early stage P22 self-assembly. A dimer formed by the C-terminal fragment of scaffolding protein with a new conformation is demonstrated to catalyze capsomer (hexamer and pentamer) aggregation efficiently. Effects of scaffolding protein/coat protein binding patterns and scaffolding protein concentration on efficiency, fidelity, and capsid curvature of P22 self-assembly are identified.

Computational Treatment of Metalloproteins

Michael R. Nechay, Crystal E. Valdez, and Anastassia N. Alexandrova [University of California, Los Angeles]

J. Phys. Chem. B., **119**, 5945–5956, 2015.

Metalloproteins present a considerable challenge for modeling, especially when the starting point is far from thermodynamic equilibrium. Examples include formidable problems such as metalloprotein folding and structure prediction upon metal addition, removal, or even just replacement; metalloenzyme design, where stabilization of a transition state of the catalyzed reaction in the specific binding pocket around the metal needs to be achieved; docking to metal-containing sites and design of metalloenzyme inhibitors.

Free Energy Calculations

Is Ring Breaking Feasible in Relative Binding Free Energy Calculations?

Shuai Liu, Lingle Wang, and David L. Mobley [University of California, Irvine]

J.Chem. Infor. and Mod. **55**, 727–735, 2015.

Our interest is relative binding free energy (RBFE) calculations based on molecular simulations. These are promising tools for lead optimization in drug discovery, computing changes in binding free energy due to modifications of a lead compound. However, in the “alchemical” framework for RBFE calculations, some types of mutations have the potential to introduce error into the computed binding free energies. Here we explore the magnitude of this error in several different model binding calculations.

Redox Potentials of Protein Disulfide Bonds from Free-Energy Calculations

Wenjin Li, Ilona B. Baldus, and Frauke Gräter [Heidelberg Institute for Theoretical Studies]

J. Phys. Chem. B., **119**, 5386–5391, 2015.

Thiol/disulfide exchange in proteins is a vital process in all organisms. To ensure specificity, the involved thermodynamics and kinetics are believed to be tailored by the structure and dynamics of the protein hosting the thiol/disulfide pair. We here aim at predicting the thermodynamics of thiol/disulfide pairs in proteins. We devise a free-energy calculation scheme, which makes use of the Crooks Gaussian intersection method to estimate the redox potential of thiol/disulfide pairs in 12 proteins belonging to the thioredoxin superfamily, namely, thioredoxins, glutaredoxins, and thiol–disulfide oxidoreductases in disulfide bond formation systems.

Ligand Binding/Docking

The unbinding studies of vascular endothelial growth factor receptor-2 protein tyrosine kinase type II inhibitors

Cong-min Kang, Dong-qing Liu, Xin-ying Wang, Ri-lei Yu, Ying-tao Lv [Qingdao University of Science and Technology]

J. Mol.Graph. and Mod., **59**, 130–135, 2015.

Vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase has two conformations, active and inactive conformations. Type II inhibitors bind to inactive conformation. It has two possible binding/unbinding paths. To explore the unbinding path of inhibitor 01-435 that was generated by fragment build in the binding pocket of VEGFR-2, molecular dynamics (MD) simulation was performed on the crystal structure of VEGFR-2 in complex with 01-435, then steered molecular dynamics (SMD) simulation was executed on the crystal structure of VEGFR-2 in complex with 01-435.

CholMine: Determinants and Prediction of Cholesterol and Cholate Binding Across Nonhomologous Protein Structures

Nan Liu, Jeffrey R. Van Voorst, John B. Johnston, and Leslie A. Kuhn [Michigan State University, East Lansing]

J.Chem. Infor. and Mod. **55**, 747–759, 2015.

Identifying physiological ligands is necessary for annotating new protein structures, yet this presents a significant challenge to biologists and pharmaceutical chemists. Here we develop a predictor of cholesterol and cholate binding that works across diverse protein families, extending beyond sequence motif-based prediction. This approach combines SimSite3D site comparison with the detection of conserved interactions in cholesterol/cholate bound crystal structures to define three-dimensional interaction motifs.

Ligand Binding / Docking (Cont'd)

In Silico and in Vitro Study of Binding Affinity of Tripeptides to Amyloid β Fibrils: Implications for Alzheimer's Disease

Man Hoang Viet, Katarina Siposova, Zuzana Bednarikova, Andrea Antosova, Truc Trang Nguyen, Zuzana Gazova, and Mai Suan Li [Polish Academy of Sciences]

J. Phys. Chem. B., **119**, 5145–5155, 2015.

Self-assembly of A β peptides into amyloid aggregates has been suggested as the major cause of Alzheimer's disease (AD). Nowadays, there is no medication for AD, but experimental data indicate that reversion of the process of amyloid aggregation reduces the symptoms of disease. In this paper, all 8000 tripeptides were studied for their ability to destroy A β fibrils. The docking method and the more sophisticated MM-PBSA (molecular mechanics Poisson–Boltzmann surface area) method were employed to calculate the binding affinity and mode of tripeptides to A β fibrils.

Enzyme Catalysis

Discovery of Potent Inhibitors of Schistosoma mansoni NAD⁺ Catabolizing Enzyme

Sylvain A. Jacques, Isabelle Kuhn, Oleksandr Koniev, Francis Schuber, Frances E. Lund, Alain Wagner, Hélène Muller-Steffner, and Esther Kellenberger [MEDALIS Drug Discovery Center]

J. Med. Chem., **58**, 3582–3592, 2015.

The blood fluke *Schistosoma mansoni* is the causative agent of the intestinal form of schistosomiasis (or bilharzia). Emergence of *Schistosoma mansoni* with reduced sensitivity to praziquantel, the drug currently used to treat this neglected disease, has underlined the need for development of new strategies to control schistosomiasis. Our ability to screen drug libraries for antischistosomal compounds has been hampered by the lack of validated *S. mansoni* targets. In the present work, we describe a virtual screening approach to identify inhibitors of *S. mansoni* NAD⁺ catabolizing enzyme (SmNACE), a receptor enzyme suspected to be involved in immune evasion by the parasite at the adult stage.

Screening of novel inhibitors targeting lactate dehydrogenase A via four molecular docking strategies and dynamics simulations

Rong Sun, Xin Li, Yuanyuan Li, Xun Zhang, Xinru Li, Xiaoyu Li, Zheng Shi, Jinku Bao [Sichuan University, Chengdu]

J. Mol. Mod., **21**, 133, 2015.

Lactate dehydrogenase A (LDHA) is a metabolic enzyme which catalyzes the interconversion of lactate and pyruvate in the glycolysis pathway, thus playing key roles in aerobic glycolysis. The inhibition of LDHA by small molecules has become an attractive strategy for anticancer therapy in recent years. However, very few LDHA inhibitors have been reported, even though a great deal of effort has directed into identifying LDHA inhibitors using structure-based approaches. In the present work, after establishing that our docking strategies performed well using test datasets, we screened 32791 Specs products for their docking scores with the substrate-binding pocket and, separately, the cofactor-binding pocket of LDHA.

Enzyme Catalysis (Cont'd)

Curcumin and hydroxamate-derivative (PCI-34058) interfere with histone deacetylase I catalytic core Asp-His charge relay system: atomistic simulation studies

I. O. Omotuyi [Nagasaki University], M. O. Abiodun, K. Komolafe, O. C. Ejelonu, O. Olusanya

J. Mol.Mod., **21**, 109, 2015.

Histone deacetylases (HDACs) are representative targets for the natural and synthetic chemicals used to transform cells to confer antitumor properties. In the current study, curcumin and hydroxamate-derivative PCI-34058-bound HDAC1 were subjected to atomistic simulation. The results support the view that fitting of curcumin and PCI-34058 within the HDAC1 pocket depends on extensive interactions between the aromatic moieties of the inhibitors and the extensive network of aromatic amino acid side chains lining the pocket of HDAC1. The interaction forces a local perturbation of the coiled structures connecting the pocket residues resulting in ligand-induced tightening of the pocket.

Free Energy Surface of the Michaelis Complex of Lactate Dehydrogenase: A Network Analysis of Microsecond Simulations

Xiaoliang Pan and Steven D. Schwartz [University of Arizona]

J. Phys. Chem. B., **119**, 5430–5436, 2015.

It has long been recognized that the structure of a protein creates a hierarchy of conformations interconverting on multiple time scales. The conformational heterogeneity of the Michaelis complex is of particular interest in the context of enzymatic catalysis in which the reactant is usually represented by a single conformation of the enzyme/substrate complex. Lactate dehydrogenase (LDH) catalyzes the interconversion of pyruvate and lactate with concomitant interconversion of two forms of the cofactor nicotinamide adenine dinucleotide (NADH and NAD⁺).

Protein-Protein Interactions

Knowledge-based modeling of peptides at protein interfaces: PiPreD

Baldo Oliva and Narcis Fernandez-Fuentes [Universitat Pompeu Fabra]

Bioinformatics. **31**, 1405-1410, 2015.

Protein–protein interactions (PPIs) underpin virtually all cellular processes both in health and disease. Modulating the interaction between proteins by means of small (chemical) agents is therefore a promising route for future novel therapeutic interventions. In this context, peptides are gaining momentum as emerging agents for the modulation of PPIs. We reported a novel computational, structure and knowledge-based approach to model orthosteric peptides to target PPIs: PiPreD. PiPreD relies on a precompiled and bespoke library of structural motifs, iMotifs, extracted from protein complexes and a fast structural modeling algorithm driven by the location of native chemical groups on the interface of the protein target named anchor residues.

Protein - Protein Interactions (Cont'd)

Topology-function conservation in protein–protein interaction networks

Darren Davis, Ömer Nebil Yaveroğlu, Noël Malod-Dognin, Aleksandar Stojmirovic, and Nataša Pržulj [Imperial College London, London]

Bioinformatics. **31**, 1632-1639, 2015.

Proteins underlay the functioning of a cell and the wiring of proteins in protein–protein interaction network (PIN) relates to their biological functions. Proteins with similar wiring in the PIN (topology around them) have been shown to have similar functions. To improve our understanding of topology-function relationships and of their conservation among species, we develop a statistical framework that is built upon canonical correlation analysis. Using the graphlet degrees to represent the wiring around proteins in PINs and gene ontology (GO) annotations to describe their functions, our framework: (i) characterizes statistically significant topology-function relationships in a given species, and (ii) uncovers the functions that have conserved topology in PINs of different species, which we term topologically orthologous functions.

Molecular Dynamics Simulations of Ternary Complexes: Comparisons of LEAFY Protein Binding to Different DNA Motifs

Hua Wan, Shan Chang [Jiangsu University of Technology], Jian-ping Hu, Yuan-xin Tian, and Xu-hong Tian

J.Chem. Infor. and Mod. **55**, 784–794, 2015.

LEAFY (LFY) is a plant-specific transcription factor, with a variety of roles in different species. LFY contains a conserved DNA-binding domain (DBD) that determines its DNA-binding specificity. Recently, the structures of the dimeric LFY-DBD bound to different DNA motifs were successively solved by X-ray crystallography. In this article, molecular dynamics (MD) simulations are employed to study two crystal structures of DNA-bound LFY protein from angiosperms and the moss *Physcomitrella patens*, respectively. The comparison of stabilities of the two systems is consistent with the experimental data of binding affinities.

Membrane Proteins and Lipid Peptide Interactions

Characterization of the Lipid-Binding Site of Equinatoxin II by NMR and Molecular Dynamics Simulation

Daniel K. Weber, Shenggen Yao, Nejc Rojko, Gregor Anderluh, Terry P. Lybrand, Matthew T. Downton, John Wagner, Frances Separovic [University of Melbourne, Victoria]

Biophysical Journal. **108**, 1987-1996, 2015.

Equinatoxin II (EqII) is a soluble, 20 kDa pore-forming protein toxin isolated from the sea anemone *Actinia equina*. Although pore formation has long been known to occur in distinct stages, including monomeric attachment to phospholipid membranes followed by detachment of the N-terminal helical domain and oligomerization into the final pore assembly, atomistic-level detail of the protein-lipid interactions underlying these events remains elusive. Using high-resolution solution state NMR of uniformly-¹⁵N-labeled EqII at the critical micelle concentration of dodecylphosphocholine, we have mapped the lipid-binding site through chemical shift perturbations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Detection and characterization of nonspecific, sparsely populated binding modes in the early stages of complexation

Antonio Cardone, Aaron Bornstein, Harish C. Pant, Mary Brady, Ram Sriram and Sergio A. Hassan [National Institutes of Health, Bethesda]

J. Comp. Chem., **36**, 983–995, 2015.

A method is proposed to study protein–ligand binding in a system governed by specific and nonspecific interactions. Strong associations lead to narrow distributions in the proteins configuration space; weak and ultraweak associations lead instead to broader distributions, a manifestation of nonspecific, sparsely populated binding modes with multiple interfaces. The method is based on the notion that a discrete set of preferential first-encounter modes are metastable states from which stable (prerelaxation) complexes at equilibrium evolve. The method can be used to explore alternative pathways of complexation with statistical significance and can be integrated into a general algorithm to study protein interaction networks.

Continuum electrostatic approach for evaluating positions and interactions of proteins in a bilayer membrane

Chirayut Supunyabut, Sunit Fuklang, Pornthep Sompornpisut [Chulalongkorn University]

J. Mol.Graph. and Mod., **59**, 81-91, 2015.

Orientations of proteins in the membranes are crucial to their function and stability. Unfortunately the exact positions of these proteins in the lipid bilayer are mostly undetermined. Here, the spatial orientation of membrane proteins within the lipid membrane was evaluated using a Poisson–Boltzmann solvent continuum approach to calculate the electrostatic free energy of the protein solvation at various orientations in an implicit bilayer. The solvation energy was obtained by computing the difference in electrostatic energies of the protein in water and in lipid/water environments, treating each as an implicit solvent model.

Structural effects of tachyplesin I and its linear derivative on their aggregation and mobility in lipid bilayers

Eol Han, Hwankyu Lee [Dankook University, Yongin]

J. Mol.Graph. and Mod., **59**, 123-128, 2015.

We performed coarse-grained molecular dynamics simulations of tachyplesin I (TP-I), which is a β -hairpin antimicrobial peptide with two disulfide bonds, and its linearly extended derivative without disulfide bonds (TPA4) in lipid bilayers for 5 μ s. β -hairpin TP-I peptides tend to individually bind to the bilayer surface, while linear TPA4 peptides aggregate and form the β -strand complex on the bilayer surface, indicating the effect of the peptide structure on aggregation. Also, TPA4 more slowly diffuse along the bilayer surface than do TP-I, indicating that aggregated β -strands of TPA4 cannot diffuse as fast as individual β -hairpins of TP-I. TPA4 have the stronger charge interaction with lipid head groups than do TP-I, leading to the deeper insertion into the bilayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Phase-transition properties of glycerol–dipalmitate lipid bilayers investigated using molecular dynamics simulation

Monika Laner, Philippe H. Hünenberger [Laboratory of Physical Chemistry, ETH Zürich]

J. Mol.Graph. and Mod., **59**, 136-147, 2015.

The phase- and phase-transition properties of glycerol–dipalmitate (GDP) bilayer patches are investigated using MD simulations. This permits to characterize the influence of introducing a second aliphatic lipid tail by comparison to previously reported simulations of glycerol-1-monopalmitate (GMP). To this purpose, a set of 67 simulations (up to 300 ns duration) of $2 \times 8 \times 8$ GDP bilayer patches are performed, considering the two GDP isomers glycerol-1,3-dipalmitate (13 GDP) and glycerol-1,2-dipalmitate (12 GDP; racemic), two hydration levels (12GDP only), and temperatures in the range 250–370 K.

Effects on lipid bilayer and nitrogen distribution induced by lateral pressure

Yu Wang, Liang Chen, Xiaogang Wang, Chaoqing Dai, Junlang Chen [Zhejiang A & F University]

J. Mol.Mod., **21**, 120, 2015.

The lateral pressure exerted on cell membrane is of great importance to signal transduction. Here, we perform molecular dynamics simulation to explore how lateral pressure affects the biophysical properties of lipid bilayer as well as nitrogen distribution in the membrane. Our results show that both physical properties of cell membrane and nitrogen distribution are highly sensitive to the lateral pressure. With the increasing lateral pressure, area per lipid drops and thickness of membrane increases obviously, while nitrogen molecules are more congested in the center of lipid bilayer than those under lower lateral pressure.

Self-Assembly Molecular Dynamics Simulations Shed Light into the Interaction of the Influenza Fusion Peptide with a Membrane Bilayer

Bruno L. Victor, Diana Lousa, Jorge M. Antunes, and Cláudio M. Soares [Universidade Nova de Lisboa]

J.Chem. Infor. and Mod. **55**, 795–805, 2015.

Influenza virus is one of the most devastating human pathogens. In order to infect host cells, this virus fuses its membrane with the host membrane in a process mediated by the glycoprotein hemagglutinin. During fusion, the N-terminal region of hemagglutinin, which is known as the fusion peptide (FP), inserts into the host membrane, promoting lipid mixing between the viral and host membranes. Therefore, this peptide plays a key role in the fusion process, but the exact mechanism by which it promotes lipid mixing is still unclear. To shed light into this matter, we performed MD simulations of the influenza FP in different environments.

Multi-Step Protocol for Automatic Evaluation of Docking Results Based on Machine Learning Methods—A Case Study of Serotonin Receptors 5-HT₆ and 5-HT₇

Sabina Smusz, Stefan Mordalski, Jagna Witek, Krzysztof Rataj, Rafał Kafel, and Andrzej J. Bojarski [Polish Academy of Sciences]

J.Chem. Infor. and Mod. **55**, 823–832, 2015.

Molecular docking, despite its undeniable usefulness in computer-aided drug design protocols and the increasing sophistication of tools used in the prediction of ligand–protein interaction energies, is still connected with a problem of effective results analysis. In this study, a novel protocol for the automatic evaluation of numerous docking results is presented, being a combination of Structural Interaction Fingerprints and Spectrophores descriptors, machine-learning techniques, and multi-step results analysis. Evaluation using compounds active toward 5-HT₆ and 5-HT₇ receptors, as well as additional analysis carried out for beta-2 adrenergic receptor ligands.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Computational Lipidomics with insane: A Versatile Tool for Generating Custom Membranes for Molecular Simulations

Tsjerk A. Wassenaar [University of Groningen, Nijenborgh 7], Helgi I. Ingólfsson, Rainer A. Böckmann, D. Peter Tieleman, and Siewert J. Marrink

J. Chem. Theor. and Comp., **11**, 2144–2155, 2015.

For simulations of membranes and membrane proteins, the generation of the lipid bilayer is a critical step in the setup of the system. Membranes comprising multiple components pose a particular challenge, because the relative abundances need to be controlled and the equilibration of the system may take several microseconds. Here we present a comprehensive method for building membrane containing systems, characterized by simplicity and versatility. The program uses preset, coarse-grain lipid templates to build the membrane, and also allows on-the-fly generation of simple lipid types by specifying the headgroup, linker, and lipid tails on the command line.

Constant-pH MD Simulations of an Oleic Acid Bilayer

Diogo Vila-Viçosa, Vitor H. Teixeira, António M. Baptista, and Miguel Machuqueiro [Universidade de Lisboa]

J. Chem. Theor. and Comp., **11**, 2367–2376, 2015.

Oleic acid is a simple molecule with an aliphatic chain and a carboxylic group whose ionization and, consequently, intermolecular interactions are strongly dependent on the solution pH. The titration curve of these molecules was already obtained using different experimental methods, which have shown the lipid bilayer assemblies to be stable between pH 7.0 and 9.0. In this work, we take advantage of our recent implementations of periodic boundary conditions in Poisson–Boltzmann calculations and ionic strength treatment in simulations of charged lipid bilayers, and we studied the ionization dependent behavior of an oleic acid bilayer using a new extension of the stochastic titration constant-pH MD method.

A Ring to Rule Them All: The Effect of Cyclopropane Fatty Acids on the Fluidity of Lipid Bilayers

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

J. Phys. Chem. B., **119**, 5487–5495, 2015.

Cyclopropane fatty acids are widespread in bacteria. As their concentration increases on exposure to hostile environments, they have been proposed to protect membranes. Here, the effect of cyclopropane and unsaturated fatty acids, both in cis and trans configurations, on the packing, order, and fluidity of lipid bilayers is explored using molecular dynamics simulations. It is shown that cyclopropane fatty acids disrupt lipid packing, favor the occurrence of gauche defects in the chains, and increase the lipid lateral diffusion, suggesting that they enhance fluidity.

Structural Properties of the Water/Membrane Interface of a Bilayer Built of the E. coli Lipid A

Krzysztof Murzyn [Jagiellonian University, Kraków] and Marta Pasenkiewicz-Gierula

J. Phys. Chem. B., **119**, 5846–5856, 2015.

Lipid A is the most chemically invariant part of lipopolysaccharides (LPS). Both lipid A and LPS constitute the external layer of the outer membrane of Gram-negative bacteria. E. coli-specific hexacyl lipid A (ECLA) forms stable bilayers in the presence of sodium or magnesium cations. To characterize biologically relevant properties of the ECLA bilayer, and in particular its water/membrane interface, 800 ns molecular dynamics (MD) simulations of fully hydrated bilayers made of ECLA at 50 °C (i.e., 6 °C above the main phase transition) were performed.

Protein Folding

Mechanisms for the synthesis of conjugated enynes from diphenylacetylene and trimethylsilylacetylene catalyzed by a nickel(0) complex: DFT study of ligand-controlled selectivity

Cheng Huang, Rongxing He, Wei Shen, Ming Li [Southwest University, Chongqing]

J. Mol.Mod., **21**, 135, 2015.

DSS1 is a small acidic intrinsically disordered protein (IDP) that can fold upon binding with PCID2 TREX-2. The resulting complex plays a key role in mRNA export. However, the binding mechanism between DSS1 and PCID2 is unsolved. Here, three independent 500-ns molecular dynamics (MD) simulations were performed to study the DSS1–PCID2 binding mechanism by comparing apo-PCID2 and bound PCID2. The results show that the conformational variation of bound PCID2 is smaller than that of apo-PCID2, especially in the binding domain of two helices (helix IV and VIII).

A theoretical study of the unfolding pathway of reduced Human serum albumin

Guillaume Paris, Christophe Ramseyer, Mironel Enescu [Université de Franche-Comté]

J. Mol.Mod., **21**, 106, 2015.

The unfolding of the reduced human serum albumin (HSA) was simulated by generating four molecular dynamics (MD) trajectories of 160 ns each at 350, 375, 400, and 425 K, respectively. A principal components analysis (PCA) was performed on the four trajectories. Based on this analysis, 17 representative protein conformers were identified and subsequently used to construct a sequence of partially unfolded structures. They were ordered according to their decreasing α -helix fractions. The structural evolution in this unfolding sequence was found to be continuous at global but also at local level supporting the hypothesis that the protein unfolding pathway is not significantly dependent on the simulation temperature.

Protein-Nucleic acid Interactions

A coarse-grained MARTINI-like force field for DNA unzipping in nanopores

Anna Stachiewicz[Adam Mickiewicz University] and Andrzej Molski

J. Comp. Chem., **36**, 947–956, 2015.

In nanopore force spectroscopy (NFS) a charged polymer is threaded through a channel of molecular dimensions. When an electric field is applied across the insulating membrane, the ionic current through the nanopore reports on polymer translocation, unzipping, dissociation, and so forth. We present a new model that can be applied in molecular dynamics simulations of NFS. Although simplified, it does reproduce experimental trends and all-atom simulations. The scaled conductivities in bulk solution are consistent with experimental results for NaCl for a wide range of electrolyte concentrations and temperatures.

Nucleic Acids

Stacking Free Energies of All DNA and RNA Nucleoside Pairs and Dinucleoside-Monophosphates Computed Using Recently Revised AMBER Parameters and Compared with Experiment

Reid F. Brown, Casey T. Andrews, and Adrian H. Elcock
[University of Iowa, Iowa City]

J. Chem. Theor. and Comp., **11**, 2315–2328, 2015.

We report the results of a series of 1- μ s-long explicit-solvent molecular dynamics (MD) simulations performed to compare the free energies of stacking (ΔG_{stack}) of all possible combinations of DNA and RNA nucleoside (NS) pairs and dinucleoside-monophosphates (DNMPs). For both NS pairs and DNMPs, we show that the computed stacking free energies are in reasonable qualitative agreement with experimental measurements and appear to provide the closest correspondence with experimental data yet found among computational studies; in all cases, however, the computed stacking free energies are too favorable relative to experimental data.

Programmable DNA-Mediated Multitasking Processor

Jian-Jun Shu [Nanyang Technological University], Qi-Wen Wang, Kian-Yan Yong, Fangwei Shao, and Kee Jin Lee

J. Phys. Chem. B., **119**, 5639–5644, 2015.

Because of DNA appealing features as perfect material, including minuscule size, defined structural repeat and rigidity, programmable DNA-mediated processing is a promising computing paradigm, which employs DNAs as information storing and processing substrates to tackle the computational problems. The massive parallelism of DNA hybridization exhibits transcendent potential to improve multitasking capabilities and yield a tremendous speed-up over the conventional electronic processors with stepwise signal cascade.

2. METHODOLOGY

Potentials and Parameters

RedMDStream: Parameterization and Simulation Toolbox for Coarse-Grained Molecular Dynamics Models

Filip Leonarski, Joanna Trylska [University of Warsaw, Warsaw]

Biophysical Journal. **108**, 1843-1847, 2015.

Coarse-grained (CG) models in molecular dynamics (MD) are powerful tools to simulate the dynamics of large biomolecular systems on micro- to millisecond timescales. However, the CG model, potential energy terms, and parameters are typically not transferable between different molecules and problems. So parameterizing CG force fields, which is both tedious and time-consuming, is often necessary. We present RedMDStream, a software for developing, testing, and simulating biomolecules with CG MD models.

Potentials and Parameters (Cont'd)

New ways to boost molecular dynamics simulations

Elmar Krieger[Centre for Molecular and Biomolecular Informatics, Radboudumc] and Gert Vriend

J. Comp. Chem., **36**, 996–1007, 2015.

We describe a set of algorithms that allow to simulate dihydrofolate reductase (DHFR, a common benchmark) with the AMBER all-atom force field at 160 nanoseconds/day on a single Intel Core i7 5960X CPU (no graphics processing unit (GPU), 23,786 atoms, particle mesh Ewald (PME), 8.0 Å cutoff, correct atom masses, reproducible trajectory, CPU with 3.6 GHz, no turbo boost, 8 AVX registers). The new features include a mixed multiple time-step algorithm (reaching 5 fs), a tuned version of LINCS to constrain bond angles, the fusion of pair list creation and force calculation, pressure coupling with a “densostat,” and exploitation of new CPU instruction sets like AVX2.

Parametrization of Backbone Flexibility in a Coarse-Grained Force Field for Proteins (COFFDROP) Derived from All-Atom Explicit-Solvent Molecular Dynamics Simulations of All Possible Two-Residue Peptides

Tamara Frembgen-Kesner, Casey T. Andrews, Shuxiang Li, Nguyet Anh Ngo, Scott A. Shubert, Aakash Jain, Oluwatoni J. Olayiwola, Mitch R. Weishaar, and Adrian H. Elcock [University of Iowa, Iowa City]

J. Chem. Theor. and Comp., **11**, 2341–2354, 2015.

Recently, we reported the parametrization of a set of coarse-grained (CG) nonbonded potential functions, derived from all-atom explicit-solvent molecular dynamics (MD) simulations of amino acid pairs and designed for use in (implicit-solvent) Brownian dynamics (BD) simulations of proteins; this force field was named COFFDROP (COarse-grained Force Field for Dynamic Representations Of Proteins). Here, we describe the extension of COFFDROP to include bonded backbone terms derived from fitting to results of explicit-solvent MD simulations of all possible two-residue peptides containing the 20 standard amino acids, with histidine modeled in both its protonated and neutral forms.

Further Efforts Toward a Molecular Dynamics Force Field for Simulations of Peptides in 40% Trifluoroethanol–Water

John T. Gerig [University of California, Santa Barbara]

J. Phys. Chem. B., **119**, 5163–5175, 2015.

A set of force field parameters for trifluoroethanol (TFE) was shown in earlier work from this lab to give a good accounting of system density, translational diffusion coefficients, and the solvent fluorine–solute hydrogen NMR cross-relaxation parameter (Σ_{HF}) for acetate dissolved in 40% TFE–water. It has since been found that this parameter set performs poorly when used to predict Σ_{HF} for interactions of TFE with the hydrogens of an octapeptide, [val⁵]angiotensin. In the present work, adjustment of nonbonded force field parameters for interactions of fluorine with hydrogen was explored with the goal of improving these predictions. Six sets of TFE parameters were examined.

Molecular Dynamics

Optogenetic versus Electrical Stimulation of Human Cardiomyocytes: Modeling Insights

John C. Williams, Emilia Entcheva [Stony Brook University, Stony Brook]

Biophysical Journal. **108**, 1934-1945, 2015.

Optogenetics provides an alternative to electrical stimulation to manipulate membrane voltage, and trigger or modify action potentials (APs) in excitable cells. We compare biophysically and energetically the cellular responses to direct electrical current injection versus optical stimulation mediated by genetically expressed light-sensitive ion channels, e.g., Channelrhodopsin-2 (ChR2). Using a computational model of ChR2(H134R mutant), we show that both stimulation modalities produce similar-in-morphology APs in human cardiomyocytes, and that electrical and optical excitability vary with cell type in a similar fashion.

Coarse-Grained Model of SNARE-Mediated Docking

Nicole Fortoul, Pankaj Singh, Chung-Yuen Hui, Maria Bykhovskaia, Anand Jagota [Lehigh University, Bethlehem]

Biophysical Journal. **108**, 2258-2269, 2015.

Synaptic transmission requires that vesicles filled with neurotransmitter molecules be docked to the plasma membrane by the SNARE protein complex. The SNARE complex applies attractive forces to overcome the long-range repulsion between the vesicle and membrane. To understand how the balance between the attractive and repulsive forces defines the equilibrium docked state we have developed a model that combines the mechanics of vesicle/membrane deformation with an apparently new coarse-grained model of the SNARE complex.

Disulfide-Mediated β -Strand Dimers: Hyperstable β -Sheets Lacking Tertiary Interactions and Turns

Brandon L. Kier, Jordan M. Anderson, and Niels H. Andersen [University of Washington, Seattle]

J. Am. Chem. Soc., **137**, 5363–5371, 2015.

Disulfide bonds between cysteine residues are essential to the structure and folding of many proteins. Yet their role in the design of structured peptides and proteins has frequently been limited to use as intrachain covalent staples that reinforce existing structure or induce knot-like conformations. In β -hairpins, their placement at non-H-bonding positions across antiparallel strands has proven useful for achieving fully folded positive controls. Here we report a new class of designed β -sheet peptide dimers with strand-central disulfides as a key element.

Comparison of structural, thermodynamic, kinetic and mass transport properties of Mg^{2+} ion models commonly used in biomolecular simulations

Maria T. Panteva, George M. Giambaşu and Darrin M. York [Rutgers University, Piscataway]

J. Comp. Chem., **36**, 970–982, 2015.

The prevalence of Mg^{2+} ions in biology and their essential role in nucleic acid structure and function has motivated the development of various Mg^{2+} ion models for use in molecular simulations. The present work addresses the first step in which we compare 17 different nonbonded single-site Mg^{2+} ion models with respect to their ability to simultaneously reproduce structural, thermodynamic, kinetic and mass transport properties in aqueous solution. None of the models based on a 12-6 nonelectrostatic nonbonded potential was able to reproduce the experimental radial distribution function, solvation free energy, exchange barrier and diffusion constant.

Molecular Dynamics (Cont'd)

Recovery of the wild type atomic flexibility in the HIV-1 protease double mutants

Valderes De Conto, Antônio S.K. Braz, David Perahia, Luis P.B. Scott [Universidade Federal do ABC]

J. Mol. Graph. and Mod., **59**, 107-116, 2015.

The emergence of drug resistant mutations due to the selective pressure exerted by antiretrovirals, including protease inhibitors (PIs), remains a major problem in the treatment of AIDS. During PIs therapy, the occurrence of primary mutations in the wild type HIV-1 protease reduces both the affinity for the inhibitors and the viral replicative capacity compared to the wild type (WT) protein, but additional mutations compensate for this reduced viral fitness. To investigate this phenomenon from the structural point of view, we combined Molecular Dynamics and Normal Mode Analysis to analyze and compare the variations of the flexibility of C-alpha atoms and the differences in hydrogen bond (h-bond) network between the WT and double mutants.

Understanding the Structure-Function Relationship of Lysozyme Resistance in *Staphylococcus aureus* by Peptidoglycan O-Acetylation Using Molecular Docking, Dynamics, and Lysis Assay

Anju C. Pushkaran, Namrata Nataraj, Nisha Nair, Friedrich Götz, Raja Biswas, and C. Gopi Mohan [Amrita Vishwa Vidyapeetham University]

J.Chem. Infor. and Mod. **55**, 760–770, 2015.

Lysozyme is an important component of the host innate defense system. It cleaves the β -1,4 glycosidic bonds between N-acetylmuramic acid and N-acetylglucosamine of bacterial peptidoglycan and induce bacterial lysis. *Staphylococcus aureus* (*S. aureus*), an opportunistic commensal pathogen, is highly resistant to lysozyme, because of the O-acetylation of peptidoglycan by O-acetyl transferase (*oatA*). This could have conferred reduced survival of the *S. aureus* *oatA* mutant in different human biological fluids. Consistent with this computational analysis, the experimental data confirmed decrease in the growth, lysozyme induced lysis, and lysozyme resistance, due to peptidoglycan O-acetylation in *S. aureus*.

Molecular Dynamics Simulations of KirBac1.1 Mutants Reveal Global Gating Changes of Kir Channels

Tobias Linder, Shizhen Wang, Eva-Maria Zangerl-Plessl, Colin G. Nichols, and Anna Stry-Weinzinger [Washington University School of Medicine]

J.Chem. Infor. and Mod. **55**, 814–822, 2015.

Prokaryotic inwardly rectifying (KirBac) potassium channels are homologous to mammalian Kir channels. Their activity is controlled by dynamical conformational changes that regulate ion flow through a central pore. Understanding the dynamical rearrangements of Kir channels during gating requires high-resolution structure information from channels crystallized in different conformations and insight into the transition steps, which are difficult to access experimentally. In this study, we use MD simulations on wild type KirBac1.1 and an activatory mutant to investigate activation gating of KirBac channels.

Molecular Dynamics (Cont'd)

An Accurate Metalloprotein-Specific Scoring Function and Molecular Docking Program Devised by a Dynamic Sampling and Iteration Optimization Strategy

Fang Bai, Sha Liao, Junfeng Gu, Hualiang Jiang, Xicheng Wang, and Honglin Li [East China University of Science and Technology]

J.Chem. Infor. and Mod. **55**, 833–847, 2015.

Metalloproteins, particularly zinc metalloproteins, are promising therapeutic targets, and recent efforts have focused on the identification of potent and selective inhibitors of these proteins. However, the ability of current drug discovery and design technologies, such as molecular docking and molecular dynamics simulations, to probe metal–ligand interactions remains limited because of their complicated coordination geometries and rough treatment in current force fields. Herein we introduce a robust, multiobjective optimization algorithm-driven metalloprotein-specific docking program named MpSDock, which runs on a scheme similar to consensus scoring consisting of a force-field-based scoring function and a knowledge-based scoring function.

Computation and Simulation of the Structural Characteristics of the Kidney Urea Transporter and Behaviors of Urea Transport

Zhe Wang, Tao Yu, Jian-Ping Sang, Xian-Wu Zou, Chengfei Yan, and Xiaoqin Zou [University of Missouri, Columbia]

J. Phys. Chem. B., **119**, 5124–5131, 2015.

Urea transporters are a family of membrane proteins that transport urea molecules across cell membranes and play important roles in a variety of physiological processes. Although the crystal structure of bacterial urea channel dvUT has been solved, there lacks an understanding of the dynamics of urea transport in dvUT. In this study, by using molecular dynamics simulations, Monte Carlo methods, and the adaptive biasing force approach, we built the equilibrium structure of dvUT, calculated the variation in the free energy of urea, determined the urea-binding sites of dvUT, gained insight into the microscopic process of urea transport, and studied the water permeability in dvUT including the analysis of a water chain in the pore.

Carboxylate Ion Pairing with Alkali-Metal Ions for β -Lactoglobulin and Its Role on Aggregation and Interfacial Adsorption

Frank R. Beierlein, Timothy Clark[Friedrich-Alexander-Universität Erlangen-Nürnberg], Björn Braunschweig, Kathrin Engelhardt, Lena Glas, and Wolfgang Peukert

J. Phys. Chem. B., **119**, 5505–5517, 2015.

We report a combined experimental and computational study of the whey protein β -lactoglobulin (BLG) in different electrolyte solutions. Vibrational sum-frequency generation (SFG) and ellipsometry were used to investigate the molecular structure of BLG modified air–water interfaces as a function of LiCl, NaCl, and KCl concentrations. Molecular dynamics (MD) simulations and thermodynamic integration provided details of the ion pairing of protein surface residues with alkali-metal cations. Our results at pH 6.2 indicate that BLG at the air–water interface forms mono- and bilayers preferably at low and high ionic strength, respectively.

Free Energy Perturbation

Accurate Calculation of Solvation Free Energies in Supercritical Fluids by Fully Atomistic Simulations: Probing the Theory of Solutions in Energy Representation

Andrey I. Frolov [Russian Academy of Sciences, Akademicheskaya St. 1]

J. Chem. Theor. and Comp., **11**, 2245–2256, 2015.

Accurate calculation of solvation free energies (SFEs) is a fundamental problem of theoretical chemistry. In this work we perform a careful validation of the theory of solutions in energy representation (ER method) developed by Matubayasi et al. [*J. Chem. Phys.* **2000**, 113, 6070–6081] for SFE calculations in supercritical solvents. This method can be seen as a bridge between the molecular simulations and the classical (not quantum) density functional theory (DFT) formulated in energy representation. We performed extensive calculations of SFEs of organic molecules of different chemical natures in pure supercritical CO₂ (sc-CO₂) and in sc-CO₂ with addition of 6 mol % of ethanol, acetone, and n-hexane as cosolvents.

Reconstructing Multiple Free Energy Pathways of DNA Stretching from Single Molecule Experiments

Eric W. Frey, Jingqiang Li, Sithara S. Wijeratne, and Ching-Hwa Kiang [Rice University, Houston]

J. Phys. Chem. B., **119**, 5132–5135, 2015.

Free energy landscapes provide information on the dynamics of proteins and nucleic acid folding. It has been demonstrated that such landscapes can be reconstructed from single molecule force measurement data using Jarzynski's equality, which requires only stretching data. However, when the process is reversible, the Crooks fluctuation theorem combines both stretch and relaxation force data for the analysis and can offer more rapid convergence of free energy estimates of different states. Here we demonstrate that, similar to Jarzynski's equality, the Crooks fluctuation theorem can be used to reconstruct the full free energy landscapes.

Accurate Calculation of Conformational Free Energy Differences in Explicit Water: The Confinement–Solvation Free Energy Approach

Jeremy Esque and Marco Cecchini [Université de Strasbourg]

J. Phys. Chem. B., **119**, 5194–5207, 2015.

The calculation of the free energy of conformation is key to understanding the function of biomolecules and has attracted significant interest in recent years. Here, we present an improvement of the confinement method that was designed for use in the context of explicit solvent MD simulations. The development involves an additional step in which the solvation free energy of the harmonically restrained conformers is accurately determined by multistage free energy perturbation simulations.

QM and QM/MM

Bacterial nitric oxide reductase: a mechanism revisited by an ONIOM (DFT:MM) study

Amr A. A. Attia, Radu Silaghi-Dumitrescu [Babeş-Bolyai University]

J. Mol.Mod., **21**, 130, 2015.

Bacterial nitric oxide reductase (cNOR) is an important binuclear iron enzyme responsible for the reduction of nitric oxide to nitrous oxide in the catalytic cycle of bacterial respiration. The reaction mechanism of cNOR as well as the key reactive intermediates of the reaction are still under debate. Here, we report a computational study based on ONIOM (DFT:MM) calculations aimed at investigating the reaction mechanism of cNOR. The results suggest that the reaction proceeds via the mono-nitrosyl mechanism which starts off by the binding of an NO molecule to the heme b3 center, N-N hyponitrite bond formation as a result of the reaction with a second NO molecule was found to proceed with an exothermic energy barrier to yield a hyponitrite adduct forming an open (incomplete) ring conformation with the non-heme Fe_B center (O-N-N-O-Fe_B).

How Y357F, Y276F mutants affect the methylation activity of PRDM9: QM/MM MD and free energy simulations

Yuzhuo Chu, Lu Sun, Shijun Zhong [Dalian University of Technology]

J. Mol.Mod., **21**, 125, 2015.

Histone methyltransferase PRDM9 catalyzes the methylation of H3K4me2 (histone 3 dimethylated lysine 4) to H3K4me3 (histone 3 trimethylated lysine 4) by transferring the methyl group from S-adenosyl methionine (AdoMet). PRDM9 is the major determinant of the meiotic recombination hotspot and the enrichment of H3K4me3 at the hotspot defines the initiation site of meiotic recombination. In PRDM9, two conserved tyrosine residues Tyr357 and Tyr276 surrounding the amino group of the substrate lysine may influence the methylation activity through hydrogen bond interactions with AdoMet or the substrate lysine.

Mechanisms for the synthesis of conjugated enynes from diphenylacetylene and trimethylsilylacetylene catalyzed by a nickel(0) complex: DFT study of ligand-controlled selectivity

Cheng Huang, Rongxing He, Wei Shen, Ming Li [Southwest University, Chongqing]

J. Mol.Mod., **21**, 135, 2015.

A quantum mechanics-based scoring function for halogen bonding interaction, namely XBScore^{QM}, is developed based on 18,135 sets of geometrical and energetical parameters optimized at M06-2X/aug-cc-pVDZ level. Applying the function on typical halogen bonding systems from Protein Data Bank demonstrates its strong ability of predicting halogen bonding as attractive interaction with strength up to -4 kcal mol^{-1} . With a diverse set of proteins complexed with halogenated ligands, a systematic evaluation demonstrates the integrative advantage of XBScore^{QM} over 12 other scoring functions on halogen bonding in four aspects, viz. pseudo docking power, ranking power, scoring power, and genuine docking power.

QM and QM/MM (Cont'd)

Theoretical Characterization of the Flavin-Based Fluorescent Protein iLOV and its Q489K Mutant

Maria G. Khrenova [M.V. Lomonosov Moscow State University], Alexander V. Nemukhin

J. Phys. Chem. B., **119**, 5176–5183, 2015.

The iLOV protein is one of the most promising members of the family of engineered flavin-based fluorescent proteins (FbFPs), considered as an alternative to the green fluorescent protein family. We modeled the spectral properties of iLOV using quantum chemistry, quantum mechanics/molecular mechanics (QM/MM), and molecular dynamics approaches. Computational results predict that the conserved Gln489 side chain in iLOV adopts two almost equally populated conformations, Gln_{in} and Gln_{out}, altering hydrogen bonding near the flavin chromophore.

A Light-Induced Reaction with Oxygen Leads to Chromophore Decomposition and Irreversible Photobleaching in GFP-Type Proteins

Bella L. Grigorenko, Alexander V. Nemukhin [M. V. Lomonosov Moscow State University], Igor V. Polyakov, Maria G. Khrenova, and Anna I. Krylov

J. Phys. Chem. B., **119**, 5444–5452, 2015.

Photobleaching and photostability of proteins of the green fluorescent protein (GFP) family are crucially important for practical applications of these widely used biomarkers. On the basis of simulations, we propose a mechanism for irreversible bleaching in GFP-type proteins under intense light illumination. The key feature of the mechanism is a photoinduced reaction of the chromophore with molecular oxygen (O₂) inside the protein barrel leading to the chromophore's decomposition. Using quantum mechanics/molecular mechanics (QM/MM) modeling we show that a model system comprising the protein-bound Chro⁻ and O₂ can be excited to an electronic state of the intermolecular charge-transfer (CT) character (Chro⁺····O₂⁻).

Comparative or Homology Modeling

In-silico analysis of the structure and binding site features of an α -expansin protein from mountain papaya fruit (VpEXPA2), through molecular modeling, docking, and dynamics simulation studies

Carlos Gaete-Eastman, Luis Morales-Quintana, Raúl Herrera, María Alejandra Moya-León [Universidad de Talca]

J. Mol.Mod., **21**, 115, 2015.

Fruit softening is associated to cell wall modifications produced by a set of hydrolytic enzymes and proteins. Expansins are proteins with no catalytic activity, which have been associated with several processes during plant growth and development. A role for expansins has been proposed during softening of fruits, and many fruit-specific expansins have been identified in a variety of species. A 3D model for VpEXPA2, an α -expansin involved in softening of *Vasconcellea pubescens* fruit, was built for the first time by comparative modeling strategy. The model was validated and refined by molecular dynamics simulation.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 59, June, 2015.

- 1-13 **Interactions between Bcl-xl and its inhibitors: Insights into ligand design from molecular dynamics simulation**, Prerna Priya, Atanu Maity, Sarmistha Majumdar, Shubhra Ghosh Dastidar [Bioinformatics Centre, Bose Institute]

See Applications / Protein Conformational Analysis.

- 14-20 **Second-order nonlinear optical properties of dithienophenazine and TTF derivatives: A butterfly effect of dimalonitrile substitutions**, Shabbir Muhammad [King Khalid University]

Using density functional theory (DFT) methods, the nonlinear optical (NLO) properties have been calculated with strong donor- π -conjugation-acceptor configurations. The static first hyperpolarizability (β_0) and dynamic (frequency dependent) electric field induced second harmonic generation (EFISHG) first hyperpolarizability ($\mu\beta$) are calculated for all designed systems.

- 21-30 **Configurational study of amino-functionalized silica surfaces: A density functional theory modeling**, Samira Hozhabr Araghi, Mohammad H. Entezari [Ferdowsi University of Mashhad], Mohammad Sadegh Sadeghi Googheri

Despite extensive studies of the amino-functionalized silica surfaces, a comprehensive investigation of the effects of configuration and hydrolysis of 3-aminopropyltriethoxysilan (APTES) molecules attached on silica has not been studied yet. Five different categories based on the number of hydrolyzed ethoxy groups including 16 configurations were designed and analyzed by the density functional theory (DFT) method.

- 31-39 **Theoretical design and simulation of supramolecular polymer unit based on multiple hydrogen bonds**, Haijie Shi, Fengdi Wang, Wei Chen, Shuwei Tang, Wanqiao Zhang, Wenliang Li, Hao Sun, Jingping Zhang, Rongshun Wang [Northeast Normal University]

The heterocyclic urea of deazapterin (**DeAPa**) and its protomeric conformers (**b**, **c**) with different substituents are selected as the building block for a series of dimers in different configurations. The stabilities of all dimers in various conditions have been investigated by density functional theory. Homodimer of **b** has more stability than other dimers.

- 40-49 **Theoretical investigation of the interaction between aromatic sulfur compounds and [BMIM]⁺[FeCl₄]⁻ ionic liquid in desulfurization: A novel charge transfer mechanism**, Hongping Li, Wenshuai Zhu, Yonghui Chang, Wei Jiang, Ming Zhang, Sheng Yin, Jiexiang Xia, Huaming Li [Jiangsu University, Zhenjiang]

In this work, interaction nature between a group of aromatic sulfur compounds and [BMIM]⁺[FeCl₄]⁻ have been investigated by density functional theory (DFT). A coordination structure is found to be critical to the mechanism of extractive desulfurization.

- 50-58 **Theoretical investigations into the electronic structures and electron transport properties of fluorine and carbonyl end-functionalized quarterthiophenes**, Qian Li, Yuai Duan, Hong-Ze Gao, Zhong-Min Su, Yun Geng [Northeast Normal University]

In this work, we concentrate on systematic investigation on the fluorination and carbonylation effect on electron transport properties of thiophene-based materials with the aim of seeking and designing electron transport materials.

- 59-71 **Aldose reductase inhibitors for diabetic complications: Receptor induced atom-based 3D-QSAR analysis, synthesis and biological evaluation**, Bhawna Vyas [Punjabi University, Patiala], Manjinder Singh, Maninder Kaur, Malkeet Singh Bahia, Amteshwar Singh Jaggi, Om Silakari, Baldev Singh

See Applications / QSAR.

- 72-80 **The role of Ir₄ cluster in enhancing the adsorption of CO₂ on selected zeolites – GCMC simulations**, Daniel Smykowski, Kacper Nowak, Rafał Łużny, Jerzy Szczygieł, Bartłomiej M. Szyja [Westfälische Wilhelms-Universität Münster]

We have investigated the adsorption of CO₂ molecules inside the EMT, SAO, SBS, SBT and IWS zeolites with respect to the influence of the Ir₄ clusters on the adsorption capabilities of these materials. We have determined that the capabilities of CO₂ adsorption depend on the combined effect of the framework topology and the position of the Ir₄ cluster.

- 81-91 **Continuum electrostatic approach for evaluating positions and interactions of proteins in a bilayer membrane**, Chirayut Supunabut, Sunit Fuklang, Pornthep Sompornpisut [Chulalongkorn University]

See Applications / Membrane Proteins.

- 92-99 **Evolution of structure, stability, and nonlinear optical properties of the heterodinuclear CNLi_n (n = 1–10) clusters**, Dan Hou, Di Wu, Wei-Ming Sun, Ying Li [Jilin University], Zhi-Ru Li

The lowest-energy structures and stabilities of the heterodinuclear clusters, CNLi_n (n = 1–10) and relevant CNLi_n⁺ (n = 1–10) cations, are studied using the density functional theory with the 6-311 + G(3df) basis set. The CNLi₆ and CNLi₅⁺ clusters are the first three-dimensional ones in the CNLi_n^{0/+} series, respectively, and the CN group always caps the Li_n^{0/+} moiety in the CNLi_n^{0/+} (n = 1–9) configurations.

- 100-106 **Theoretical investigation of self-assembled donor–acceptor phthalocyanine complexes and their application in dye-sensitized solar cells**, Lijuan Yu, Li Lin, Yuwen Liu, Renjie Li [Wuhan University]

A theoretical investigation of self-assembled donor–acceptor dyads (**ZnPca**, **ZnPcb** and **ZnPcc**) formed by axial coordination of zinc phthalocyanines appended with 4-carboxyl pyridine has been conducted with the density functional theory (DFT) method and time-dependent DFT (TD-DFT) calculations.

- 107-116 **Recovery of the wild type atomic flexibility in the HIV-1 protease double mutants**, Valderes De Conto, Antônio S.K. Braz, David Perahia, Luis P.B. Scott [Universidade Federal do ABC]

See Methodology / Molecular Dynamics.

- 117-122 **Molecular docking study of macrocycles as Fk506-binding protein inhibitors**, Corey A. MacDonald, Russell J. Boyd [Dalhousie University]

See Applications / Medicinal Chemistry and Drug Design.

- 123-128 **Structural effects of tachyplesin I and its linear derivative on their aggregation and mobility in lipid bilayers**, Eol Han, Hwankyoo Lee [Dankook University, Yongin]

See Applications / Membrane Proteins.

- 130-135 **The unbinding studies of vascular endothelial growth factor receptor-2 protein tyrosine kinase type II inhibitors**, Cong-min Kang, Dong-qing Liu, Xin-ying Wang, Ri-lei Yu, Ying-tao Lv [Qingdao University of Science and Technology]

See Applications / Ligand Binding.

- 136-147 **Phase-transition properties of glycerol–dipalmitate lipid bilayers investigated using molecular dynamics simulation**, Monika Laner, Philippe H. Hünenberger [Laboratory of Physical Chemistry, ETH Zürich]

See Applications / Membrane Proteins.

Journal of Computational Chemistry, 36 (12), May, 2015.

- 871–877 **Toward the complete range separation of non-hybrid exchange–correlation functional**, Bun Chan [University of Sydney, Australia], Jong-Won Song, Yukio Kawashima and Kimihiko Hirao

In this study, we use a very simple scheme to achieve range separation of a total exchange–correlation functional. We have utilized this methodology to combine a short-range pure density functional theory (DFT) functional with a corresponding long-range pure DFT, leading to a “Range-separated eXchange–Correlation” (RXC) scheme.

- 878–882 **Fep1d: A script for the analysis of reaction coordinates**, Polina V. Banushkina and Sergei V. Krivov [University of Leeds]

The dynamics of complex systems with many degrees of freedom can be analyzed by projecting it onto one or few coordinates (collective variables). The dynamics is often described then as diffusion on a free energy landscape associated with the coordinates. Fep1d is a script for the analysis of such one-dimensional coordinates.

- 883–890 **The topology of the Ehrenfest force density revisited. A different perspective based on Slater-type orbitals**, Jan Dillen [Department of Chemistry and Polymer Science, Private Bag X1, Matieland]

The topology of the Ehrenfest force density was studied with Slater-type orbitals (STO). At larger distances from the nuclei, STOs generate similar artefacts as noticed before with Gaussian-type orbitals. The topology of the Ehrenfest force density was found to be mainly homeomorphic with the topology of the electron

density. For the first time, reliable integrations of several properties over force density atomic basins were performed successfully.

- 891–900 **Theoretical comparative studies on transport properties of pentacene, pentathienoacene, and 6,13-dichloropentacene**, Xu Zhang, Xiaodi Yang, Hua Geng, Guangjun Nan, Xingwen Sun, Jinyang Xi and Xin Xu [Fudan University, Shanghai]

Pentacene derivative 6,13-dichloropentacene (DCP) is one of the latest additions to the family of organic semiconductors with a great potential for use in transistors. We carry out a detailed theoretical calculation for DCP, with systematical comparison to pentacene, pentathienoacene (PTA, the thiophene equivalent of pentacene), to gain insights in the theoretical design of organic transport materials.

- 901–906 **The behavior of benzene confined in a single wall carbon nanotube**, Yury D. Fomin, Elena N. Tsiok and Valentin N. Ryzhov [Institute for High Pressure Physics Russian Academy of Sciences]

We present the molecular dynamics study of benzene molecules confined into the single wall carbon nanotube. The local structure and orientational ordering of benzene molecules are investigated.

- 907–925 **State-specific multireference perturbation theory with improved virtual orbitals: Taming the ground state of F_2 , Be_2 , and N_2** , Sudip Chattopadhyay [Indian Institute of Engineering Science and Technology, Howrah], Rajat K. Chaudhuri and Uttam Sinha Mahapatra

Adaptation of improved virtual orbitals (IVOs) in state-specific multireference perturbation theory using Møller–Plesset multipartitioning of the Hamiltonian (IVO-SSMRPT) is examined in which the IVO-complete active space configuration interaction (CASCI) is used as an inexpensive alternative to the more involved CAS-self-consistent field (CASSCF) orbitals.

- 926–933 **The performance of low-cost commercial cloud computing as an alternative in computational chemistry**, Russell Thackston and Ryan C. Fortenberry [Georgia Southern University]

The growth of commercial cloud computing (CCC) as a viable means of computational infrastructure is largely unexplored for the purposes of quantum chemistry. In this work, the PSI4 suite of computational chemistry programs is installed on five different types of Amazon World Services CCC platforms. The performance for a set of electronically excited state single-point energies is compared between these CCC platforms and typical, “in-house” physical machines.

- 934–939 **Why many semiempirical molecular orbital theories fail for liquid water and how to fix them**, Matthew Welborn, Jiahao Chen, Lee-Ping Wang and Troy Van Voorhis [Massachusetts Institute of Technology, Cambridge]

Water is an extremely important liquid for chemistry and the search for more accurate force fields for liquid water continues unabated. Using force matching, we design a reparameterized NDDO model and find that it qualitatively reproduces the experimental radial distribution function of water, as well as various monomer, dimer, and bulk properties that PM6 does not.

Journal of Computational Chemistry, 36 (13), May, 2015.

947–956 **A coarse-grained MARTINI-like force field for DNA unzipping in nanopores**, Anna Stachiewicz[Adam Mickiewicz University] and Andrzej Molski

See Applications / Protein-Nucleic acids.

957–969 **Symmetry classification of electron and phonon states in TiO₂-based nanowires and nanotubes**, Robert A. Evarestov and Andrej I. Panin [St.-Petersburg State University]

Procedure for deriving Wyckoff positions for nanowires (NWs) and nanotubes (NTs) from Wyckoff positions of ambient space group is described. It is proposed how to use SITESYM code available on Bilbao Crystallographic Server to calculate representations induced from orbit stabilizers for 1-periodic groups.

970–982 **Comparison of structural, thermodynamic, kinetic and mass transport properties of Mg²⁺ ion models commonly used in biomolecular simulations**, Maria T. Panteva, George M. Giambaşu and Darrin M. York [Rutgers University, Piscataway]

See Methodology / Molecular Dynamics.

983–995 **Detection and characterization of nonspecific, sparsely populated binding modes in the early stages of complexation**, Antonio Cardone, Aaron Bornstein, Harish C. Pant, Mary Brady, Ram Sriram and Sergio A. Hassan [National Institutes of Health, Bethesda]

See Applications / Membrane Proteins.

996–1007 **New ways to boost molecular dynamics simulations**, Elmar Krieger[Centre for Molecular and Biomolecular Informatics, Radboudumc] and Gert Vriend

See Methodology / Potentials and Parameters.

1008–1014 **Bonding charge density from atomic perturbations**, Yi Wang [The Pennsylvania State University], William Yi Wang, Long-Qing Chen and Zi-Kui Liu

Charge transfer among individual atoms is the key concept in modern electronic theory of chemical bonding. In this work, we present a first-principles approach to calculating the charge transfer.

Journal of Computational Chemistry, 36 (14), May, 2015.

1029–1035 **Are the reduction and oxidation properties of nitrocompounds dissolved in water different from those produced when adsorbed on a silica surface? A DFT M05-2X computational study**, Liudmyla K. Sviatenko, Olexandr Isayev, Leonid Gorb, Frances C. Hill, Danuta Leszczynska and Jerzy Leszczynski [Jackson State University, Jackson]

The reduction and oxidation properties of four nitrocompounds (trinitrotoluene [TNT], 2,4-dinitrotoluene, 2,4-dinitroanisole, and 5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one [NTO]) dissolved in water as compared with the same properties for compounds adsorbed on a silica surface were studied.

- 1036–1046**A cascaded QSAR model for efficient prediction of overall power conversion efficiency of all-organic dye-sensitized solar cells**, Hongzhi Li, Ziyang Zhong, Lin Li, Rui Gao, Jingxia Cui, Ting Gao, Li Hong Hu, Yinghua Lu, Zhong-Min Su and Hui Li [Northeast Normal University, Changchun]

A cascaded model is proposed to establish the quantitative structure–activity relationship (QSAR) between the overall power conversion efficiency (PCE) and quantum chemical molecular descriptors of all-organic dye sensitizers.

- 1047–1059**LS-VISM: A software package for analysis of biomolecular solvation**, Shenggao Zhou [University of California, San Diego], Li-Tien Cheng, Hui Sun, Jianwei Che, Joachim Dzubiella, Bo Li and J. Andrew McCammon

See Applications / Bioinformatics.

- 1060–1068**Gradient gravitational search: An efficient metaheuristic algorithm for global optimization**, Tirtharaj Dash and Prabhat K. Sahu [National Institute of Science & Technology, Berhampur]

The adaptation of novel techniques developed in the field of computational chemistry to solve the concerned problems for large and flexible molecules is taking the center stage with regard to efficient algorithm, computational cost and accuracy. In this article, the gradient-based gravitational search (GGS) algorithm, using analytical gradients for a fast minimization to the next local minimum has been reported.

- 1069–1074**Protein alignment: Exact versus approximate. An illustration**, Milan Randić [Laboratory of Chemometrics, Ljubljana] and Tomaž Pisanski

See Applications / Protein Conformational Analysis.

- 1075–1082**Revisiting the extrapolation of correlation energies to complete basis set limit**, Masaki Okoshi, Teruo Atsumi and Hiromi Nakai [Waseda University, Tokyo]

The extrapolation scheme of correlation energy is revisited to evaluate the complete basis set limit from double-zeta (DZ) and triple-zeta levels of calculations. The DZ level results are adjusted to the standard asymptotic behavior with respect to the cardinal number, observed at the higher levels of basis sets.

- 1083–1101**Robustness in the fitting of molecular mechanics parameters**, Kenno Vanommeslaeghe, Mingjun Yang and Alexander D. MacKerell Jr. [University of Maryland, Baltimore]

Automated methods for force field parametrization have attracted renewed interest of the community, but the robustness issues associated with the often ill-conditioned nature of parameter optimization have been vastly underappreciated in the recent literature. For this reason, this article offers a detailed description of the origin and nature of these issues. This includes a discussion of the restrained electrostatic potential fit (RESP) charge model, which does contain explicit robustness-enhancing measures albeit not in the context of bonded parameters, and which forms an inspiration for the present work.

Journal of Molecular Modeling, 21 (5), May, 2015.

- 135 **Mechanisms for the synthesis of conjugated enynes from diphenylacetylene and trimethylsilylacetylene catalyzed by a nickel(0) complex: DFT study of ligand-controlled selectivity**, Cheng Huang, Rongxing He, Wei Shen, Ming Li [Southwest University, Chongqing]

Density functional theory (DFT) was utilized to elucidate the reaction mechanisms of and the key factors that influence the Ni(0)-catalyzed cross-dimerization and -trimerization of trimethylsilylacetylene (R1) and diphenylacetylene (R2).

- 134 **Energetic salts from nitroformate ion**, Pandurang M. Jadhav, S. Radhakrishnan, Vikas D. Ghule [National Institute of Technology, Kurukshetra], Raj K. Pandey

Development of new energetic salts is the key factor in replacing low performance compounds in conventional formulations of high explosives as well as propellants. Ten salts based on the nitroformate anion and various nitrogen-rich cations were designed and their geometric optimizations carried out using the density functional method.

- 133 **Screening of novel inhibitors targeting lactate dehydrogenase A via four molecular docking strategies and dynamics simulations**, Rong Sun, Xin Li, Yuanyuan Li, Xun Zhang, Xinru Li, Xiaoyu Li, Zheng Shi, Jinku Bao [Sichuan University, Chengdu]

See Applications / Enzyme Catalysis.

- 132 **Explore the reaction mechanism of the Maillard reaction: a density functional theory study**, Ge-Rui Ren [Zhejiang Gongshang University], Li-Jiang Zhao, Qiang Sun, Hu-Jun Xie, Qun-Fang Lei, Wen-Jun Fang

The mechanism of Maillard reaction has been investigated by means of density functional theory calculations in the gaseous phase and aqueous solution. The Maillard reaction is a cascade of consecutive and parallel reaction. In the present model system study, glucose and glycine were taken as the initial reactants.

- 131 **The reactivity of phenacyl bromide under β -cyclodextrin as supramolecular catalyst: a computational survey**, Yali Wan, Xueye Wang [Xiangtan University, Xiangtan], Na Liu

Phenacyl bromide as one starting material in multicomponent reactions (MCRs) with β -cyclodextrin (β -CD) as catalyst can get an excellent yield in short reaction times. The interaction of β -CD with phenacyl bromide plays an important role in this process. This paper studies the complex of β -CD with phenacyl bromide using density functional theory (DFT) method.

- 130 **Bacterial nitric oxide reductase: a mechanism revisited by an ONIOM (DFT:MM) study**, Amr A. A. Attia, Radu Silaghi-Dumitrescu [Babeş-Bolyai University]

See Methodology / QM and QM/MM.

- 129 **DFT study of zinc, cadmium, mercury, copper, silver, and gold complexes of 21,23-dioxaporphyrin and one-dimensional arrays of those complexes**, Ulises Jiménez Castillo, Héctor López, Patricia Guadarrama, Serguei Fomine [Universidad Nacional Autónoma de México]

Complexes of 21,23-dioxaporphyrin with neutral Zn, Cd, Hg, Cu, Ag, and Au atoms as well as some one-dimensional arrays of those complexes containing up to ten repeat units were modeled at the PBE/def2-TZVPP level of theory with D3 empirical dispersion correction.

- 128 **Development of a coarse-grained α -chitin model on the basis of MARTINI forcefield**, Zechuan Yu, Denvi Lau [City University of Hong Kong]

See Applications / Protein Structure Analysis.

- 127 **Conformational stability of PCID2 upon DSS1 binding with molecular dynamics simulation**, Qianjun Liu, Guodong Hu, Zanzia Cao, Jihua Wang [Dezhou University, Dezhou], Haifeng Chen

See Applications / Protein Folding.

- 126 **Molecular stacking character and charge transport properties of tetrabenzoseptacenes derivatives: the effects of nitrogen doping and phenyl substitution**, Lin Guan, Wenliang Wang [Shaanxi Normal University, Xi'an], Rong Shao, Fengyi Liu, Shiwei Yin

The nitrogen doping and phenyl substitution effects on the geometries, molecular stacking character, electronic, and charge transport properties of tetrabenzoseptacene (TTBH) have been investigated by means of density functional theory (DFT) calculation and incoherent charge hopping model.

- 125 **How Y357F, Y276F mutants affect the methylation activity of PRDM9: QM/MM MD and free energy simulations**, Yuzhuo Chu, Lu Sun, Shijun Zhong [Dalian University of Technology]

See Methodology / QM and QM/MM.

- 124 **Retention-time prediction for polycyclic aromatic compounds in reversed-phase capillary electrochromatography**, Peter Feenstra, Heidrun Gruber-Wölfler, Michael Brunsteiner, Johannes Khinast [Graz University of Technology]

Log $P_{o/w}$ based models are often used for the retention time prediction of reversed phase liquid chromatography. Here, we present the investigation of the applicability of log $P_{o/w}$ based retention time predictions for the separation in capillary electrochromatography (CEC). A test set of five polycyclic aromatic hydrocarbons was separated using two different stationary phases with three different mobile phases each.

- 123 **Conformational behavior of polyalanine peptides with and without protecting groups of varying chain lengths: population of PP-II structure!**, Fateh S. Nandel [Panjab University, Chandigarh], Mohan L. Garg, Mohd Shafique

See Applications / Protein Conformational Analysis.

- 122 **A computational study on the insertion of CO₂ into (PSiP)palladium allyl σ -bond**, Qin Wang, Cai-Hong Guo, Ying Ren, Hai-Shun Wu [Shanxi Normal University, Linfen]

The insertion of CO₂ into the (PSiP)palladium-allyl bond has been investigated using DFT. Three possible modes of CO₂ insertion into (PSiP)Pd-allyl bond have been calculated, that is, direct 1,2-insertion mode, metallo-ene mode, and S_E2 mode.

- 121 **Interfacial adhesion between functionalized polyethylene surface and graphene via molecular dynamic simulation**, S. Javan Nikkhah, M. R. Moghbeli [Iran University of Science and Technology], S. M. Hashemianzadeh

In this study, interfacial adhesion between functionalized polyethylene (PE) surfaces and graphene were examined using molecular simulation. Various functional groups including amino, carboxy, hydroxy, cyano, isocyanato, oxo, and ethylamino were used to cover the PE surface with surface densities of 0.48, 1.30, and 4.84 groups per nm².

- 120 **Effects on lipid bilayer and nitrogen distribution induced by lateral pressure**, Yu Wang, Liang Chen, Xiaogang Wang, Chaoqing Dai, Junlang Chen [Zhejiang A & F University]

See Applications / Membrane Proteins.

- 119 **Rovibrational energy and spectroscopic constant calculations of complexes pairing via dihydrogen bonds**, Mohammad Solimannejad [Arak University, Arak], Hamidreza Jouypazadeh, Hossein Farokhpour

In the present investigation, we performed a thorough study of potential energy curves, rovibrational spectra, and spectroscopic constants for complexes pairing via dihydrogen bonds. In particular, we dealt with LiH...HX (X = F, CN, CCH, CCF, CCCI) complexes by employing accurate electronic energy calculations at the MP2/aug-cc-pVDZ level of theory.

- 118 **Time-dependent density functional theory calculations of the solvatochromism of some azo sulfonamide fluorochromes**, Przemysław Krawczyk [Nicolaus Copernicus University]

The absorption and emission spectra of three azo sulfonamide compounds in different solvents were investigated theoretically by using response functions combined with density functional theory (DFT), while the solvent effect on the structure and the electronic transitions was determined using the integral equation formalism for the polarizable continuum model (IEF-PCM).

- 117 **Interaction of OH⁻ with xylan and its hydrated complexes: structures and molecular dynamics study using elongation method**, Lin Jin, Kai Liu, Yuriko Aoki [Kyushu University, 6-1 Kasuga-Park]

The interaction of OH⁻ group with (xylan)₁₂ and its hydrated complexes were theoretically studied using elongation optimization (ELG-OPT) method and elongation ab initio molecular dynamics simulation (ELG-MD) method.

- 116 **Adsorption of carbon monoxide on the pristine, B- and Al-doped C₃N nanosheets**, Mansoureh Pashangpour, Ali Ahmadi Peyghan [Islamic Azad University, Tehran]

The potential application of the intrinsic and extrinsic (8,0) zigzag single-walled C₃N nanosheets as chemical sensor for CO molecules has been investigated using density functional theory calculations. The calculation shows that the pristine sheet is a semiconductor with a HOMO-LUMO gap (E_g) of about 2.19 eV.

- 115 **In-silico analysis of the structure and binding site features of an α -expansin protein from mountain papaya fruit (VpEXPA2), through molecular modeling, docking, and dynamics simulation studies,** Carlos Gaete-Eastman, Luis Morales-Quintana, Raúl Herrera, María Alejandra Moya-León [Universidad de Talca]

See Methodology / Homology Modeling.

- 114 **A theoretical study on the strength of the C–NO₂ bond and ring strain upon the formation of the intermolecular H-bonding interaction between HF and nitro group in nitrocyclopropane, nitrocyclobutane, nitrocyclopentane or nitrocyclohexane,** Wei Qiu [Harbin Institute of Technology, Harbin], Fu-de Ren, Wen-jing Shi, Yan-hong Wang

As a follow-up to our investigation into the influence of H-bond on the C–NO₂ trigger bond, a comparison of the effect of the H-bond on the ring strain energy with the C–NO₂ bond dissociation energy was carried out in the HF complex with nitrocyclopropane, nitrocyclobutane, nitrocyclopentane, and nitrocyclohexane by using the DFT-B3LYP and MP2 (full) methods with the 6–311++G(2df,2p) and aug-cc-pVTZ basis sets.

- 113 **Parameterization for molecular Gaussian surface and a comparison study of surface mesh generation,** Tiantian Liu, Minxin Chen, Benzhuo Lu [Chinese Academy of Sciences, Beijing]

The molecular Gaussian surface has been frequently used in the field of molecular modeling and simulation. Typically, the Gaussian surface is defined using two controlling parameters; the decay rate and isovalue. In this paper, surface area, volume enclosed by the surface and Hausdorff distance are used as three criteria for the parameterization to make the Gaussian surface approximate the solvent excluded surface (SES) well.

- 112 **Comparison of halogen bonds in M–X $\cdots$ N contacts (M=C, Si, Ge and X=Cl, Br),** Hossein Jalali Jahromi [Islamic Azad University], Kiamars Eskandari, Azam Alizadeh

The halogen bonds (XB) formed between some Si–X- and Ge–X- (X is Cl and Br) containing molecules and NCH (as a Lewis base) have been investigated and compared with C–X $\cdots$ N halogen bond.

- 111 **Quantum chemical study of the isomerization of 24-methylenecycloartanol, a potential marker of olive oil refining,** Henry B. Wedler, Ryan P. Pemberton, Valère Lounnas, Gert Vriend, Dean J. Tantillo, Selina C. Wang [CMBI Radboudumc]

Quantum chemical calculations on the isomerization of 24-methylenecycloartanol are described. An energetically viable mechanism, with a rate-determining protonation step, is proposed. This rearrangement may find applicability in tests for determining if an olive oil has been refined.

- 109 **Curcumin and hydroxamate-derivative (PCI-34058) interfere with histone deacetylase I catalytic core Asp-His charge relay system: atomistic simulation studies,** I. O. Omotuyi [Nagasaki University], M. O. Abiodun, K. Komolafe, O. C. Ejelonu, O. Olusanya

See Applications / Enzyme Catalysis.

- 108 **Theoretical study of spectroscopic constants and anharmonic force field of SiF₂,** Jing Li, Meishan Wang [Ludong University, Yantai], Chuanlu Yang, Meizhong Ma, Dianmin Tong

The equilibrium structure, spectroscopy constants, and anharmonic force field of SiF₂ have been investigated at MP2, B3LYP, and B3PW91 levels of theory employing two basis sets cc-pVQZ and cc-pVTZ, respectively.

- 106 **A theoretical study of the unfolding pathway of reduced Human serum albumin**, Guillaume Paris, Christophe Ramseyer, Mironel Enescu [Université de Franche-Comté]

See Applications / Protein Folding.

- 105 **On the interactions of leflunomide and teriflunomide within receptor cavity — NMR studies and energy calculations**, Jacek Kujawski [Poznan University of Medical Sciences], Marek K. Bernard, Elżbieta Jodłowska, Kornelia Czaja, Beata Drabińska

Leflunomide is a disease-modifying antirheumatic drug with antiinflammatory and immunosuppressive activity used for the treatment of psoriatic and rheumatoid arthritis. Continuing our investigations on the interactions of biologically important azahetarenes with the environment, we focused on leflunomide and its active metabolite, teriflunomide, considering the interactions teriflunomide–amino acid within the target protein (dihydroorotate dehydrogenase) using density functional theory, as well as ONIOM techniques.

- 104 **Understanding the role of the trifluoromethyl group in reactivity and regioselectivity in [3+2] cycloaddition reactions of enol acetates with nitrones. A DFT study**, Hatem Layeb, Abdelmalek Khorief Nacereddine, Abdelhafid Djerourou, Mar Ríos-Gutiérrez, Luis R. Domingo [Universidad de Valencia]

The mechanism of the [3+2] cycloaddition (32CA) reaction of C-phenyl-N-methylnitrone with ethyl trifluoroacetoacetate has been theoretically studied at the MPWB1K/6-311G(d,p) level. This 32CA reaction, in which the enol form of the β -keto ester participates as the ethylene component, takes place with complete ortho regioselectivity and exo stereoselectivity.

Journal of Molecular Modeling, 21 (6), June, 2015.

- 143 **A comprehensive analysis of P $\cdots\pi$ pnictogen bonds: substitution effects and comparison with Br $\cdots\pi$ halogen bonds**, Cuicui Liu, Yanli Zeng, Xiaoyan Li, Lingpeng Meng, Xueying Zhang [Hebei Normal University]

Ab initio calculations were carried out in a systematic investigation of P $\cdots\pi$ pnictogen-bonded complexes XH₂P $\cdots$ C₂H₂/C₂H₄ and FH₂P $\cdots$ C₂R₂/C₂R₄ for X = H, CH₃, OH, CN, Br, Cl, NO₂, F, and R = F, CH₃, as well as corresponding Br $\cdots\pi$ halogen-bonded complexes XBr $\cdots$ C₂H₂.

- 142 **Quantum chemical investigation on the role of Li adsorbed on anatase (101) surface nano-materials on the storage of molecular hydrogen**, V. Srinivasadesikan, P. Raghunath, M. C. Lin [National Chiao Tung University]

Lithiation of TiO₂ has been shown to enhance the storage of hydrogen up to 5.6 wt% (Hu et al. J Am Chem Soc 128:11740–11741, 2006). The mechanism for the process is still unknown. In this work we have carried out a study on the adsorption and diffusion of Li atoms on the surface and migration into subsurface layers of anatase (101) by periodic density functional theory calculations implementing on-site Coulomb interactions (DFT+U).

- 141 Comparative study of small boron, silicon and germanium clusters: B_mSi_n and B_mGe_n ($m + n = 2-4$),** Leonardo T. Ueno, Valéria O. Kiohara, Luiz F. A. Ferrão, Marina Pelegrini, Orlando Roberto-Neto, Francisco B. C. Machado [Instituto Tecnológico de Aeronáutica, São José dos Campos]

Chemically speaking, atomic clusters are very rich, allowing their application in a broad range of technological areas such as developing functional materials, heterogeneous catalysis, and building optical devices. In this work, high level computational chemistry methods were used in a systematic manner to improve the characterization of small clusters formed by boron, silicon, germanium, mixed boron/silicon, and mixed boron/germanium.

- 140 Computational simulation study on the anion recognition properties of functionalized tetraphenyl porphyrins,** Ju Xie, Xuesong Chen, Zhiling Huang, Tongfei Zuo [Yangzhou University]

The anion recognitions of tetra-(2-formamido) phenyl porphyrin (APP), tetra-(2-ureido) phenyl porphyrin (UPP), and their zinc derivatives (ZnAPP and ZnUPP) to three anions (Cl^- , $H_2PO_4^-$, CH_3COO^-) were studied using quantum mechanical calculations (QM) and molecular dynamics (MD) simulations.

- 139 The bond force constant and bulk modulus of small fullerenes using density functional theory and finite element analysis,** A. Tapia [Universidad Autónoma de Yucatán], C. Villanueva, R. Peón-Escalante, R. Quintal, J. Medina, F. Peñuñuri, F. Avilés

Dedicated bond force constant and bulk modulus of C_n fullerenes ($n = 20, 28, 36, 50, 60$) are computed using density functional theory (DFT). DFT predicts bond force constants of 611, 648, 675, 686, and 691 N/m, for C_{20} , C_{28} , C_{36} , C_{50} , and C_{60} , respectively, indicating that the bond force constant increases for larger fullerenes.

- 138 A quantum mechanics-based halogen bonding scoring function for protein-ligand interactions,** Zhuo Yang, Yingtao Liu, Zhaoqiang Chen, Zhijian Xu, Jiye Shi, Kaixian Chen, Weiliang Zhu [Shanghai Institute of Materia Medica]

See Methodology / QM and QM/MM.

- 137 Elucidation of hydroxyl groups-antioxidant relationship in mono- and dihydroxyflavones based on O-H bond dissociation enthalpies,** Witcha Treesuwan [Kasetsart University], Songwut Suramitr, Supa Hannongbua

Radical scavenging potential is the key to anti-oxidation of hydroxyflavones which generally found in fruits and vegetables. The objective of this work was to investigate the influence of hydroxyl group on the O-H bond dissociation enthalpies (BDE) from a series of mono- and dihydroxyflavones.

- 136 Aromaticity of the completely annelated tetraphenylenes: NICS and GIMIC characterization,** Gleb V. Baryshnikov [Bogdan Khmelnsky National University], Nataliya N. Karaush, Rashid R. Valiev, Boris F. Minaev

A series of heterocyclic and hydrocarbon [8]circulenes (also named completely annelated tetraphenylenes) were studied by the NICS and GIMIC methods in order to describe their aromatic properties from the magnetic criterion point of view.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

A. Tapia
jorge.tapia@uady.mx
Facultad de Ingeniería,
Universidad Autónoma de
Yucatán,
Av. Industrias no contaminantes
por Periférico Norte,
Cordemex, C.P. 97310, Mérida,
Yucatán, Mexico

Adrian H. Elcock
adrian-elcock@uiowa.edu
Department of Biochemistry,
University of Iowa, Iowa City,
Iowa 52242, United States

Alexander D. MacKerell Jr.
alex@outerbanks.umaryland.edu
Department of Pharmaceutical
Sciences,
School of Pharmacy,
University of Maryland, Baltimore,
Maryland

Alexander V. Nemukhin
anemukhin@yahoo.com
Department of Chemistry,
M. V. Lomonosov Moscow State
University,
Leninskie Gory 1/3, Moscow,
119991, Russian Federation

Ali Ahmadi Peyghan
ahmadi.iau@gmail.com
Young Researchers and Elite club,
Central Tehran Branch,
Islamic Azad University, Tehran,
Iran

Anand Jagota
anj6@lehigh.edu
Department of Chemical and
Biomolecular Engineering,
Lehigh University, Bethlehem,
Pennsylvania

Anastassia N. Alexandrova
ana@chem.ucla.edu
Department of Chemistry and
Biochemistry,
University of California, Los
Angeles,
Los Angeles, California 90095,
United States

Andrej I. Panin
andrej.panin@gmail.com
Chemistry Department,
St.-Petersburg State University,
St.-Petersburg, Russia

Andrey I. Frolov
andrey.i.frolov@mail.ru
Institute of Solution Chemistry,
Russian Academy of Sciences,
Akademicheskaya St. 1, 153045
Ivanovo, Russia

Andrzej J. Bojarski
bojarski@if-pan.krakow.pl
Department of Medicinal
Chemistry,
Institute of Pharmacology,
Polish Academy of Sciences,
12 Smętna Street, 31-343 Kraków,
Poland

Anna Stachiewicz
anna.st@amu.edu.pl
Department of Chemistry,
Adam Mickiewicz University,
Poznan, Poland

Anna Stary-Weinzinger
anna.stary@univie.ac.at
Center for Investigation of
Membrane Excitability Diseases,
Department of Cell Biology and
Physiology,
Washington University School of
Medicine,
St. Louis, Missouri 63110, United
States

Anne-Claude Camproux
anne-claude.camproux@univ-
paris-diderot.fr
INSERM, UMRS-973,
MTi, Paris, France

Bartłomiej M. Szyja
b.m.szyja@tue.nl
Institute for Solid State Theory,
Westfälische Wilhelms-Universität
Münster,
Wilhelm Klemm Str. 10,
48148 Münster, Germany

Benoît Roux
roux@uchicago.edu
Department of Biochemistry and
Molecular Biology,
Gordon Center for Integrative
Science,
University of Chicago, Chicago,
Illinois 60637, United States

Benzhuo Lu

bzlu@lsec.cc.ac.cn
State Key Laboratory of Scientific
and Engineering Computing,
National Center for Mathematics
and Interdisciplinary Sciences,
Academy of Mathematics and
Systems Science,
Chinese Academy of Sciences,
Beijing, 100190, China

Bhawna Vyas
bhawnaom@rediffmail.com
Department of Chemistry,
Punjabi University,
Patiala 147002, Punjab, India

Bun Chan
bun.chan@sydney.edu.au
School of Chemistry,
University of Sydney, Australia

C. Gopi Mohan
cgmohan@aims.amrita.edu
Amrita Centre for Nanosciences
and Molecular Medicine,
Amrita Institute of Medical
Sciences & Research Centre,
Amrita Vishwa Vidyapeetham
University,
Ponekkara, Kochi 682 041, Kerala
State, India

Ching-Hwa Kiang
chkhang@rice.edu
Department of Bioengineering,
Rice University, Houston,
Texas 77005, United States

Cláudio M. Soares
claudio@itqb.unl.pt
ITQB, Instituto de Tecnologia
Química e Biológica António
Xavier,
Universidade Nova de Lisboa,
Av. da República, 2780-157
Oeiras, Portugal

Darrin M. York
york@biomaps.rutgers.edu
Center for Integrative Proteomics
Research,
BioMaPS Institute and Department
of Chemistry & Chemical Biology,
Rutgers University, Piscataway,
New Jersey

David B. Ascher
dascher@svi.edu.au
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road, Sanger
Building,

Cambridge, Cambridgeshire CB2
1GA, U.K.

David E. Shaw
David.Shaw@DEShawResearch.co
m
D. E. Shaw Research, New York,
New York 10036, United States

David L. Mobley
dmobley@mobleylab.org
Department of Pharmaceutical
Sciences and Department of
Chemistry,
University of California, Irvine,
147 Bison Modular, Irvine,
California 92697, United States

David Poger
d.poger@uq.edu.au
School of Chemistry and
Molecular Biosciences,
The University of Queensland,
Brisbane QLD 4072, Australia

Denvi Lau
denvi@mit.edu
Department of Architecture and
Civil Engineering,
City University of Hong Kong,
Hong Kong, China

Elmar Krieger
elmar@yasara.org
Centre for Molecular and
Biomolecular Informatics,
Radboudumc, The Netherlands

Emilia Entcheva
emilia.entcheva@stonybrook.edu
Department of Biomedical
Engineering,
Stony Brook University,
Stony Brook, New York

Eran Eyal
eyal.eran@gmail.com
Cancer Research Institute,
Sheba Medical Center, 2 Sheba Rd,
Ramat Gan 52621, Israel

Esther Kellenberger
ekellen@unistra.fr
Laboratoire d'Innovation
Thérapeutique,
MEDALIS Drug Discovery Center,
Faculté de Pharmacie,
LIT UMR7200 CNRS/Université
de Strasbourg,
74 Route du Rhin, 67401 Illkirch,
France

Fateh S. Nandel

- fateh_nandel@yahoo.com
Department of Biophysics,
Panjab University, Chandigarh,
160014, India
- Frances Separovic
fs@unimelb.edu.au
School of Chemistry,
University of Melbourne, Victoria,
Australia
- Francisco B. C. Machado
fmachado@ita.br
Departamento de Química,
Instituto Tecnológico de
Aeronáutica,
São José dos Campos, 12228-900,
São Paulo, Brazil
- Frauke Gräter
frauke.graeter@h-its.org
Heidelberg Institute for Theoretical
Studies,
Schloss-Wolfsbrunnenweg 35,
69118 Heidelberg, Germany
- G. Narahari Sastry
gnsastry@gmail.com
Centre for Molecular Modeling,
Indian Institute of Chemical
Technology,
Hyderabad 500007, India
- Ge-Rui Ren
rengerui@zjgsu.edu.cn
Department of Applied Chemistry,
Zhejiang Gongshang University,
Hangzhou, 310018, China
- Gleb V. Baryshnikov
glebchem@rambler.ru
Department of Organic Chemistry,
Bogdan Khmel'nitsky National
University,
blvd. Shevchenko 81, 18031,
Cherkasy, Ukraine
- Hai-Shun Wu
wuhs@mail.sxnu.edu.cn
School of Chemistry and Materials
Science,
Shanxi Normal University, Linfen,
041004, People's Republic of
China
- Hiromi Nakai
nakai@waseda.jp
Department of Chemistry and
Biochemistry,
School of Advanced Science and
Engineering,
Waseda University, Tokyo, Japan
- Honglin Li
hlli@ecust.edu.cn
State Key Laboratory of Bioreactor
Engineering,
Shanghai Key Laboratory of New
Drug Design,
- School of Pharmacy,
East China University of Science
and Technology,
Shanghai 200237, China
- Hossein Jalali Jahromi
hossein.jalali1354@gmail.com
Department of Chemistry,
Mahshahr Branch,
Islamic Azad University,
Mahshahr, Iran
- Huaming Li
lihm@uj.s.edu.cn
Institute for Energy Research,
Jiangsu University,
Zhenjiang 212013, PR China
- Hui Li
lihui@nenu.edu.cn
School of Computer Science and
Information Technology,
Northeast Normal University,
Changchun, China
- Hwankyu Lee
leeh@dankook.ac.kr
Department of Chemical
Engineering,
Dankook University, Yongin,
448-701, South Korea
- I. O. Omotuyi
omotuyi@nagasaki-u.ac.jp
Department of Pharmacology and
Therapeutic Innovation,
Nagasaki University, 1-14 Bunkyo-
machi,
852-8531, Nagasaki, Japan
- Irwin Chaiken
ichaiken@drexelmed.edu
Biochemistry and Molecular
Biology,
Drexel University College of
Medicine,
Philadelphia, Pennsylvania 19102,
United States
- Jacek Kujawski
jacekuj@ump.edu.pl
Department of Organic Chemistry,
Faculty of Pharmacy, Poznan
University of Medical Sciences,
Grunwaldzka 6 street, 60-780,
Poznań, Poland
- Jamshed Iqbal
drjamshed@ciit.net.pk
Centre for Advanced Drug
Research,
COMSATS Institute of
Information Technology,
Abbottabad, Pakistan
- Jan Dillen
JLMD@sun.ac.za
Department of Chemistry and
Polymer Science,
- Private Bag X1, Matieland, South
Africa
- Jerzy Leszczynski
jerzy@icnanotox.org
Department of Chemistry and
Biochemistry,
Interdisciplinary Nanotoxicity
Center,
Jackson State University, Jackson,
Mississippi
- Jian-Jun Shu
mjjshu@ntu.edu.sg
School of Mechanical & Aerospace
Engineering,
Nanyang Technological University,
50 Nanyang Avenue, Singapore
639798, Singapore
- Jiangning Song
Jiangning.Song@monash.edu
Department of Biochemistry and
Molecular Biology,
Monash University, Melbourne,
VIC 3800, Australia
- Jihua Wang
jhw25336@126.com
Shandong Provincial Key
Laboratory of Functional
Macromolecular Biophysics,
College of Physics and Electronic
Information,
Dezhou University, Dezhou,
253023, China
- Jing Wang
jingwang@mdanderson.org
Departments of Bioinformatics and
Computational Biology,
Houston, TX 77030
- Jinku Bao
baojinku@scu.edu.cn
School of Life Sciences & State
Laboratory of Bio-resources and
Eco-environment,
Ministry of Education,
State Key Laboratory of
Biotherapy,
Sichuan University, Chengdu,
610065, China
- Joanna Trylska
joanna@cent.uw.edu.pl
Centre of New Technologies,
University of Warsaw, Warsaw,
Poland
- Johannes Khinast
khinast@tugraz.at
Institute of Process and Particle
Engineering,
NAWI Graz, Graz University of
Technology,
TU Graz, Inffeldgasse 13, 8010,
Graz, Austria
- John T. Gerig
gerig@chem.ucsb.edu
Department of Chemistry and
Biochemistry,
University of California, Santa
Barbara,
Santa Barbara, California 93105
United States
- Junlang Chen
chenjunlang7955@sina.com
School of Sciences,
Zhejiang A & F University,
Lin'an, 311300, China
- Krzysztof Murzyn
krzysztof.murzyn@uj.edu.pl
Department of Computational
Biophysics and Bioinformatics,
Faculty of Biochemistry,
Biophysics, and Biotechnology,
Jagiellonian University, Kraków,
Poland
- Leslie A. Kuhn
KuhnL@msu.edu
Department of Biochemistry and
Molecular Biology,
Michigan State University, East
Lansing,
Michigan 48824-1319, United
States
- Luis P.B. Scott
luisp37@gmail.com
Laboratório de Biologia
Computacional e Bioinformática,
Universidade Federal do ABC,
Santo André, SP, Brazil
- Luis R. Domingo
domingo@utopia.uv.es
Departamento de Química
Orgánica,
Universidad de Valencia, Dr.
Moliner 50,
46100, Burjassot, Valencia, Spain
- M. C. Lin
chemmcl@emory.edu
Center for Interdisciplinary
Molecular Science,
Department of Applied Chemistry,
National Chiao Tung University,
Hsinchu, 300, Taiwan
- M. R. Moghbeli
mr_moghbeli@iust.ac.ir
School of Chemical Engineering,
Iran University of Science and
Technology (IUST),
Tehran 16846-13114, Iran
- Mai Suan Li
masli@ifpan.edu.pl
Institute of Physics,
Polish Academy of Sciences,
Al. Lotnikow 32/46, 02-668
Warsaw, Poland

- Marco Cecchini
mcecchini@unistra.fr
Laboratoire d'Ingénierie des
Fonctions Moléculaires (ISIS),
UMR 7006 CNRS, Université de
Strasbourg,
F-67083 Strasbourg Cedex, France
- María Alejandra Moya-León
alemoya@utalca.cl
Laboratorio de Fisiología Vegetal y
Genética Molecular,
Instituto de Ciencias Biológicas,
Universidad de Talca, Casilla 747,
Talca, Chile
- Maria G. Khrenova
wasabiko13@gmail.com
Chemistry Department,
M.V. Lomonosov Moscow State
University,
Leninskie Gory 1/3, Moscow,
119991, Russian Federation
- Maxim Totrov
max@molsoft.com
Molsoft L.L.C., 11199 Sorrento
Valley Road,
S209, San Diego,
California 92121, United States
- Meishan Wang
mswang1971@163.com
School of Physics and
Optoelectronics Engineering,
Ludong University, Yantai,
264025, China
- Miguel Machuqueiro
machuque@ciencias.ulisboa.pt
Centro de Química e Bioquímica
and
Departamento de Química e
Bioquímica,
Faculdade de Ciências,
Universidade de Lisboa,
Edifício C8 Campo Grande,
1749-016 Lisboa, Portugal
- Milan Randić
mrandic@msn.com
National Institute of Chemistry,
Laboratory of Chemometrics,
Ljubljana, Slovenia
- Ming Li
liming@swu.edu.cn
School of Chemistry and Chemical
Engineering,
Southwest University, Chongqing,
400715, China
- Mironel Enescu
mironel.enescu@univ-fcomte.fr
Laboratoire Chrono
Environnement UMR CNRS 6249,
Faculté des Sciences et
Techniques, La Bouloie,
Université de Franche-Comté,
25030, Besançon cedex, France
- Mohammad H. Entezari
moh_entezari@yahoo.com
Sonochemical Research Center,
Department of Chemistry,
Ferdowsi University of Mashhad,
91775 Mashhad, Iran
- Mohammad Moghadasi
midas@bu.edu
Department of Biomedical
Engineering,
Boston University, Boston,
Massachusetts 02215, United
States
- Mohammad Solimannejad
m-solimannejad@araku.ac.ir
Department of Chemistry, Faculty
of Sciences,
Arak University, Arak, 38156-8-
8349, Iran
- Narcis Fernandez-Fuentes
narcis.fernandez@gmail.com
Structural Bioinformatics Lab
(GRIB),
Departament de Ciències
Experimental i de la Salut,
Universitat Pompeu Fabra, 08003
Barcelona, Spain
- Nataša Pržulj
natasha@imperial.ac.uk
Department of Computing,
Imperial College London, London,
UK
- Niels H. Andersen
andersen@chem.washington.edu
Chemistry Department,
University of Washington, Seattle,
Washington 98195, United States
- Peter J. Ortoleva
ortoleva@indiana.edu
Center for Theoretical and
Computational Nanoscience,
Department of Chemistry, Indiana
University,
Bloomington, Indiana 47405,
United States
- Peter Meinicke
peter@gobics.de
Department of Bioinformatics,
Institute for Microbiology and
Genetics,
University of Göttingen, Germany
- Philippe H. Hünenberger
phil@igc.phys.chem.ethz.ch
Laboratory of Physical Chemistry,
ETH Zürich, Zürich, Switzerland
- Pornthep Sompornpisut
spornthe@hotmail.com
Computational Chemistry Unit
Cell,
Department of Chemistry, Faculty
of Science,
Chulalongkorn University,
254 Phayathai Rd. Prathumwan,
Bangkok 10330, Thailand
- Prabhat K. Sahu
prabhat.sahu@nist.edu
Center for Multiscale Modeling,
National Institute of Science &
Technology,
Berhampur-761008, India
- Przemysław Krawczyk
przemekk@cm.umk.pl
Collegium Medicum,
Department of Physical Chemistry,
Nicolaus Copernicus University,
Kurpińskiego 5, 85-950,
Bydgoszcz, Poland
- Radhakrishnan Mahalakshmi
maha@iiserb.ac.in
Molecular Biophysics Laboratory,
Department of Biological Sciences,
Indian Institute of Science
Education and Research,
Bhopal 462023, India
- Radu Silaghi-Dumitrescu
rsilaghi@chem.ubbcluj.ro
Department of Chemistry,
Faculty of Chemistry and Chemical
Engineering,
Babeş-Bolyai University, Cluj-
Napoca, Romania
- Rebecca C. Wade
rebecca.wade@h-its.org
Molecular and Cellular Modeling
Group,
Heidelberg Institute for Theoretical
Studies,
69118 Heidelberg, Germany
- Renjie Li
lirj@whu.edu.cn
College of Chemistry and
Molecular Science,
Wuhan University,
Wuhan 430072, PR China
- Romina Oliva
romina.oliva@uniparthenope.it
Department of Sciences and
Technologies,
University "Parthenope" of Naples,
Naples, Italy
- Rongshun Wang
wangrs@nenu.edu.cn
Institute of Functional Material
Chemistry,
Faculty of Chemistry,
Northeast Normal University,
Renmin Road 5268,
- Changchun, Jilin 130024, P.R.
China
- Russell J. Boyd
russell.boyd@dal.ca
Department of Chemistry,
Dalhousie University, 62 74
Coburg Road,
Halifax, NS, Canada B3H 4R2
- Ryan C. Fortenberry
rfortenberry@georgiasouthern.edu
Department of Chemistry,
Georgia Southern University,
Statesboro, Georgia
- Selina C. Wang
scwang@ucdavis.edu
CMBI Radboudumc, Geert
Grooteplein 26-28,
6525 GA, Nijmegen, The
Netherlands
- Sergei V. Krivov
s.krivov@leeds.ac.uk
Astbury Center for Structural
Molecular Biology,
Faculty of Biological Sciences,
University of Leeds,
Leeds LS2 9JT, United Kingdom
- Sergio A. Hassan
hassan@mail.nih.gov
Division of Computational
Bioscience,
Center for Molecular Modeling,
CIT,
National Institutes of Health,
Bethesda, Maryland
- Serguei Fomine
fomine@servidor.unam.mx
Instituto de Investigaciones en
Materiales,
Universidad Nacional Autónoma
de México,
Apartado Postal 70-360, CU,
Coyoacán,
Mexico, DF, 04510, Mexico
- Shabbir Muhammad
mshabbir@kku.edu.sa
Department of Physics, College of
Science,
King Khalid University, P.O. Box
9004,
Abha 61413, Saudi Arabia
- Shan Chang
schang@jsut.edu.cn
Institute of Bioinformatics and
Medical Engineering,
School of Electrical and
Information Engineering,
Jiangsu University of Technology,
Changzhou 213001, China
- Shenggao Zhou
s4zhou@math.ucsd.edu

Department of Mathematics,
University of California,
San Diego, La Jolla, California

Shijun Zhong
sjzhong@dlut.edu.cn
School of Life Science and
Biotechnology,
Dalian University of Technology,
2 Linggong Road, Dalian,
Liaoning Province, 116024, China

Shubhra Ghosh Dastidar
sgducd@gmail.com
Bioinformatics Centre, Bose
Institute,
P-1/12 C.I.T. Scheme VII M,
Kolkata 700054, India

Steven D. Schwartz
sschwartz@email.arizona.edu
Department of Chemistry and
Biochemistry,
University of Arizona, 1306 East
University Boulevard,
Tucson, Arizona 85721, United
States

Timothy Clark
Tim.Clark@fau.de
Computer-Chemie-Centrum and
Interdisciplinary Center for
Molecular Materials,
Friedrich-Alexander-Universität
Erlangen-Nürnberg,
Nägelsbachstr. 25, 91052 Erlangen,
Germany

Tongfei Zuo
fragment_jade@163.com
College of Chemistry and
Chemical Engineering,
Yangzhou University,
Yangzhou, 225002, China

Troy Van Voorhis
tvan@mit.edu
Department of Chemistry,
Massachusetts Institute of
Technology,
Cambridge, Massachusetts

Tsjerk A. Wassenaar
tsjerkw@gmail.com
Groningen Biomolecular Sciences
and Biotechnology Institute and
Zernike Institute for Advanced
Materials,
University of Groningen,
Nijenborgh 7,
9747 AG Groningen, The
Netherlands

Valentin N. Ryzhov
ryzhov@hppt.troitsk.ru
Institute for High Pressure Physics
Russian Academy of Sciences,
Moscow, Russia

Sudip Chattopadhyay
sudip_chattopadhyay@rediffmail.c
om
Department of Chemistry,
Indian Institute of Engineering
Science and Technology,
Howrah, India

Vikas D. Ghule
gvd@nitkkr.ac.in
Department of Chemistry,
National Institute of Technology,
Kurukshetra, 136119, Haryana,
India

Vincent A. Voelz
voelz@temple.edu
Department of Chemistry, Temple
University,
Philadelphia, Pennsylvania 19122,
United States

Wei Qiu
qiuweihi@126.com
State Key Laboratory of Urban
Water Resource and Environment,
Harbin Institute of Technology,
Harbin, 150001, China

Weiliang Zhu
wlzhu@mail.shcnc.ac.cn
Drug Discovery and Design
Center,
Key Laboratory of Receptor
Research,
Shanghai Institute of Materia
Medica,
Chinese Academy of Sciences, 555
Zuchongzhi Road,
Shanghai, 201203, China

Wenliang Wang
wlwang@snnu.edu.cn
Key Laboratory for
Macromolecular Science of
Shaanxi Province,
School of Chemistry & Chemical
Engineering,
Shaanxi Normal University, Xi'an,
Shaanxi, 710062, People's
Republic of China

Witcha Treesuwan
ifrwctw@ku.ac.th
Institute of Food Research and
Product Development,
Kasetsart University,
Bangkok, 10900, Thailand

Xiaoqin Zou
zoux@missouri.edu
Dalton Cardiovascular Research
Center,
Department of Physics and
Astronomy,
Department of Biochemistry, and
Informatics Institute,
University of Missouri, Columbia,
Missouri 65211, United States

Xin Xu
xxchem@fudan.edu.cn
Department of Chemistry,
Fudan University, Shanghai, China

Xueye Wang
wxueye@xtu.edu.cn
Key Laboratory of
Environmentally Friendly
Chemistry and Applications of
Ministry of Education,
College of Chemistry, Xiangtan
University,
Xiangtan, Hunan, 411105,
People's Republic of China

Xueying Zhang
zhangxywuhua@163.com
Institute of Computational
Quantum Chemistry,
College of Chemistry and Material
Sciences,
Hebei Normal University,
Shijiazhuang, 050024, China

Yangbo Feng
yfeng@scripps.edu
Medicinal Chemistry, Translational
Research Institute,
The Scripps Research Institute,
Florida, Jupiter, FL 33458, USA

Yi Wang
Department of Materials Science
and Engineering,
The Pennsylvania State University,
Pennsylvania

Ying Li, Zhi-Ru Li
liyingedu@jlu.edu.cn
Institute of Theoretical Chemistry,
State Key Laboratory of
Theoretical and Computational
Chemistry,
Jilin University, Liutiao Road No.
2,
Changchun 130023, People's
Republic of China

Ying-tao Lv
lvyngtao@qust.edu.cn
College of Chemical Engineering,
Qingdao University of Science and
Technology,
Qingdao 266042, PR China

Yuh Min Chook
yuhmin.chook@utsouthwestern.ed
u
Department of Pharmacology,
University of Texas Southwestern
Medical Center at Dallas,
Dallas, TX 75390-9041, USA

Yun Geng
gengyun575@gmail.com
Institute of Functional Material
Chemistry,

Faculty of Chemistry, Northeast
Normal University,
Changchun 130024, Jilin,
People's Republic of China

Yuriko Aoki
aoki.yuriko.397@m.kyushu-u.ac.jp
Department of Material Sciences,
Faculty of Engineering Sciences,
Kyushu University, 6-1 Kasuga-
Park,
Fukuoka, 816-8580, Japan

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Editor:

R.Mutyala.
MMCC Results
RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.
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Assistant Editors:

Anston Feenstra, Vrije Univ., Amsterdam, Netherlands
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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Oligomerization of a Glucagon-like Peptide 1 Analog: Bridging Experiment and Simulations

Tine M. Frederiksen, Pernille Sønderby, Line A. Ryberg, Pernille Harris, Jens T. Bukrinski, Anne M. Scharff-Poulsen, Maria N. Elf-Lind, Günther H. Peters [Technical University of Denmark]

Biophysical Journal. **109**, 1202-1213, 2015.

The glucagon-like peptide 1 (GLP-1) analog, liraglutide, is a GLP-1 agonist and is used in the treatment of type-2 diabetes mellitus and obesity. From a pharmaceutical perspective, it is important to know the oligomerization state of liraglutide with respect to stability. Compared to GLP-1, liraglutide has an added fatty acid (FA) moiety that causes oligomerization of liraglutide as suggested by small-angle x-ray scattering (SAXS) and multiangle static light scattering (MALS) results. SAXS data suggested a global shape of a hollow elliptical cylinder of size hexa-, hepta-, or octamer, whereas MALS data indicate a hexamer.

Understanding the basis of I50V-induced affinity decrease in HIV-1 protease via molecular dynamics simulations using polarized force field

Rui Duan, Raudah Lazim and Dawei Zhang [Nanyang Technological University]

J. Comp. Chem., **36**, 1885–1892, 2015.

Human immunodeficiency virus (HIV)-1 protease is one of the most promising drug target commonly utilized to combat Acquired Immune Deficiency Syndrome (AIDS). However, with the emergence of drug resistance arising from mutations, the efficiency of protease inhibitors (PIs) as a viable treatment for AIDS has been greatly reduced. I50V mutation as one of the most significant mutations occurring in HIV-1 protease will be investigated in this study. Molecular dynamics (MD) simulation was utilized to examine the effect of I50V mutation on the binding of two PIs namely indinavir and amprenavir to HIV-1 protease.

 MMCC Results 8013 Los Sabalos Street San Diego, CA 92126 Tel. (858) 663-0162 e-mail: mmccresults@gmail.com Dr. R. Mutyala. RR Labs Inc., 8013 Los Sabalos St. San Diego, CA 92126 Editors Emeritus: Bruce Gelin, Ph.D. David Busath, M.D. Dr. Gelin was founder of MMCC Results and edited volumes 1-6. Dr. David Busath edited volumes 7-14	MMCC Results (ISSN 1061-6381) is published ten times per year at the beginning of each month except January and August by the independent business, MMCC Results. Mention of software, hardware, or other products is for informational purposes only and does not constitute an endorsement or recommendation by MMCC Results nor by the authors of the paper cited. All product names are the trademarks or registered symbols of their respective holders. Marginal symbols indicate that the authors acknowledged the use of a software package from a commercial source. A refers to Accelrys Inc. and T to Tripos Inc. Other companies are denoted by their name in a box. Papers of special interest are marked by an exclamation point [!]. Copyright © 2006 MMCC Results	Assistant Editors: Sowmya .N Rational Labs, Hyderabad., India Sambasivareddy M RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

Binding specificity of polypeptide substrates in NS2B/NS3pro serine protease of dengue virus type 2: A molecular dynamics Study

Pathumwadee Yotmanee, Thanyada Rungrotmongkol, Kanin Wichapong, Sy Bing Choi, Habibah A. Wahab, Nawee Kungwan, Supot Hannongbua [Chulalongkorn University, Bangkok]

J. Mol.Graph. and Mod., **60**, 24-33, 2015.

The pathogenic dengue virus (DV) is a growing global threat, particularly in South East Asia, for which there is no specific treatment available. The virus possesses a two-component (NS2B/NS3) serine protease that cleaves the viral precursor proteins. Here, we performed molecular dynamics simulations of the NS2B/NS3 protease complexes with six peptide substrates (capsid, intNS3, 2A/2B, 4B/5, 3/4A and 2B/3 containing the proteolytic site between P¹ and P^{1'} subsites) of DV type 2 to compare the specificity of the protein-substrate binding recognition.

Association of the anti-tuberculosis drug rifampicin with a PAMAM dendrimer

Reinaldo G. Bellini, Ana P. Guimarães, Marco A.C. Pacheco, Douglas M. Dias, Vanessa R. Furtado, Ricardo B. de Alencastro, Bruno A.C. Horta [Universidade Federal do Rio de Janeiro]

J. Mol.Graph. and Mod., **60**, 34-42, 2015.

The association of the anti-tuberculosis drug rifampicin (RIF) with a 4th-generation poly(amidoamine) (G4-PAMAM) dendrimer was investigated by means of molecular dynamics simulations. The RIF load capacity was estimated to be around 20 RIF per G4-PAMAM at neutral pH. The complex formed by 20 RIF molecules and the dendrimer (RIF₂₀-PAMAM) was subjected to 100 ns molecular dynamics (MD) simulations at two different pH conditions (neutral and acidic). The complex was found to be significantly more stable in the simulation at neutral pH compared to the simulation at low pH in which the RIF molecules were rapidly and almost simultaneously expelled to the solvent bulk.

Computational fishing of new DNA methyltransferase inhibitors from natural products

Wilson Maldonado-Rojas, Jesus Olivero-Verbel [University of Cartagena], Yovani Marrero-Ponce

J. Mol.Graph. and Mod., **60**, 43-54, 2015.

DNA methyltransferase inhibitors (DNMTis) have become an alternative for cancer therapies. However, only two DNMTis have been approved as anticancer drugs, although with some restrictions. Natural products (NPs) are a promising source of drugs. In order to find NPs with novel chemotypes as DNMTis, 47 compounds with known activity against these enzymes were used to build a LDA-based QSAR model for active/inactive molecules (93% accuracy) based on molecular descriptors. This classifier was employed to identify potential DNMTis on 800 NPs from NatProd Collection.

Molecular descriptors calculation as a tool in the analysis of the antileishmanial activity achieved by two series of diselenide derivatives. An insight into its potential action mechanism

María Font [Departamento de Química Orgánica y Farmacéutica], Ylenia Baquedano, Daniel Plano, Esther Moreno, Socorro Espuelas, Carmen Sanmartín, Juan Antonio Palop

J. Mol.Graph. and Mod., **60**, 63-78, 2015.

A molecular modeling study has been carried out on two previously reported series of symmetric diselenide derivatives that show remarkable antileishmanial in vitro activity against *Leishmania infantum* intracellular amastigotes and in infected macrophages (THP-1 cells), in addition to showing favorable selectivity indices. Series **1** consists of compounds that can be considered as central scaffold constructed with a diaryl/dialkylaryl diselenide central nucleus, decorated with different substituents located on the aryl rings. Series **2** consists of compounds constructed over a diaryl diselenide central nucleus, decorated in 4 and 4' positions with an aryl or heteroaryl sulfonamide fragment, thus forming the diselenosulfonamide derivatives.

Medicinal Chemistry and Drug Design (Cont'd)

The study of dual COX-2/5-LOX inhibitors by using electronic-topological approach based on data on the ligand–receptor interactions

Fatma Aksakal, Natali Shvets, Anatholy Dimoglo [Gebze Technical University, Kocaeli]

J. Mol.Graph. and Mod., **60**, 79-88, 2015.

Structural and electronic factors influencing selective inhibition of cyclooxygenase-2 and 5-lipoxygenase (COX-2/5-LOX) were studied by using Electronic-Topological Method combined with Neural Networks (ETM–NN), molecular docking, and Density Functional Theory (DFT) in a large set of molecules. The results of the ETM–NN calculations allowed for the selection of pharmacophoric molecular fragments, which could be taken as a basis for a system capable of predicting the COX-2/5-LOX inhibitory activity.

Designing of potential inhibitors against Staphylococcus aureus sortase A: Combined analogue and structure based approach with in vitro validation

K. Kranthi Raj, Veeramachaneni Ganesh Kumar, Chalasani Leela Madhuri, Pardhasaradhi Mathi, Ravulapati Durga Lakshmi, M. Ravi, B. Sri Ramudu, S.V. Venkata Rao, D. Ramachandran [Acharya Nagarjuna University]

J. Mol.Graph. and Mod., **60**, 89-97, 2015.

Staphylococcus aureus sortase A is an attractive target of Gram-positive bacteria that plays a crucial role in anchoring of surface proteins to peptidoglycan present in bacterial cell wall. Inhibiting sortase A is an elementary and essential effort in preventing the pathogenesis. In this context, in silico virtual screening of in-house database was performed using ligand based pharmacophore model as a filter. The developed pharmacophore model AAHR 11 consists of two acceptors, one hydrophobic and one ring aromatic feature. Top ranked molecule **KKR1** was docked into the active site of the target.

Structural and dynamical aspects of Streptococcus gordonii FabH through molecular docking and MD simulations

Amen Shamim, Sumra Wajid Abbasi, Syed Sikander Azam [Quaid-i-Azam University]

J. Mol.Graph. and Mod., **60**, 180-196, 2015.

β -Ketoacyl-ACP-synthase III (FabH or KAS III) has become an attractive target for the development of new antibacterial agents which can overcome the multidrug resistance. Unraveling the fatty acid biosynthesis (FAB) metabolic pathway and understanding structural coordinates of FabH will provide valuable insights to target Streptococcus gordonii for curing oral infection. In this study, we designed inhibitors against therapeutic target FabH, in order to block the FAB pathway. As compared to other targets, FabH has more interactions with other proteins, located on the leading strand with higher codon adaptation index value and associated with lipid metabolism category of COG.

Structure-Based Virtual Screening and Biological Evaluation of a Calpain Inhibitor for Prevention of Selenite-Induced Cataractogenesis in an in Vitro System

Arumugam Ramachandran Muralidharan, Chandrabose Selvaraj, Sanjeev Kumar Singh, Joen-Rong Sheu, Philip A. Thomas, and Pitchairaj Geraldine [School of Life Sciences, Bharathidasan University]

J.Chem. Infor. and Mod. **55**, 1686–1697, 2015.

Calpains belong to the family of calcium-dependent, structurally related intracellular cysteine proteases that exhibit significant functions in evolution of different types of cataracts in human as well as animal models. Application of calpain inhibitors generated through a virtual screening workflow may provide new avenues for the prevention of cataractogenesis. Hence, in the current study, compounds were first screened for potent calpain inhibitory activity by employing a structure-based approach, and the screening results were then validated through biological experiments in rat lenses.

Medicinal Chemistry and Drug Design (Cont'd)

DINTO: Using OWL Ontologies and SWRL Rules to Infer Drug–Drug Interactions and Their Mechanisms

María Herrero-Zazo [Universidad Carlos III de Madrid], Isabel Segura-Bedmar, Janna Hastings, and Paloma Martínez

J.Chem. Infor. and Mod. **55**, 1698–1707, 2015.

The early detection of drug–drug interactions (DDIs) is limited by the diffuse spread of DDI information in heterogeneous sources. Computational methods promise to play a key role in the identification and explanation of DDIs on a large scale. However, such methods rely on the availability of computable representations describing the relevant domain knowledge. Current modeling efforts have focused on partial and shallow representations of the DDI domain, failing to adequately support computational inference and discovery applications. In this paper, we describe a comprehensive ontology for DDI knowledge (DINTO), which is the first formal representation of different types of DDIs and their mechanisms and its application in the prediction of DDIs.

Discovery of Novel CXCR2 Inhibitors Using Ligand-Based Pharmacophore Models

Helen Ha, Bikash Debnath, Srinivas Odde, Tim Bensman, Henry Ho, Paul M. Beringer, and Nouri Neamati [University of Michigan, North Campus Research Complex]

J.Chem. Infor. and Mod. **55**, 1720–1738, 2015.

The chemokine receptor CXCR2 is expressed on various immune cells and is essential for neutrophil recruitment and angiogenesis at sites of acute and chronic inflammation caused by tissue injury or infection. CXCR2 and its ligand, CXCL8, are implicated in a number of inflammation-mediated diseases such as chronic obstructive pulmonary disease, cystic fibrosis, and cancer. A pharmacophore model based on previously reported CXCR2 antagonists was developed to screen a database of commercially available compounds.

POSIT: Flexible Shape-Guided Docking For Pose Prediction

Brian P. Kelley, Scott P. Brown, Gregory L. Warren [OpenEye Scientific Software], and Steven W. Muchmore

J.Chem. Infor. and Mod. **55**, 1771–1780, 2015.

We present a new approach to structure-based drug design (POSIT) rigorously built on the simple concept that pose prediction is intimately coupled to the quality and availability of experimental structural data. We demonstrate the feasibility of the approach by performing retrospective analyses on three data sets designed to explore the strengths and weaknesses of POSIT relative to existing methods. We then present results documenting 2.5 years of prospective use of POSIT across a variety of structure-based industrial drug-discovery research projects.

Destabilization of Alzheimer's A β 42 Protofibrils with a Novel Drug Candidate wxg-50 by Molecular Dynamics Simulations

Huai-Meng Fan, Ruo-Xu Gu, Yan-Jing Wang, Yun-Long Pi, Yong-Hong Zhang, Qin Xu, and Dong-Qing Wei [Shanghai Jiao Tong University]

J. Phys. Chem. B., **119**, 11196–11202, 2015.

Alzheimer's disease (AD) is one of the most common dementia. The aggregation and deposition of the amyloid- β peptide (A β) in neural tissue is its characteristic symptom. To destabilize and dissolve A β fibrils, a number of candidate molecules have been proposed. wxg-50 is a compound extracted from Sichuan pepper (*Zanthoxylum bungeanum*) and a potential candidate drug for treating AD. Our early experiments show it is effective in disassembling A β 42 aggregations. A series of molecular dynamics simulations were performed in this work to explain the molecular mechanism of the destabilization of A β 42 protofibril by wxg-50.

Host-Guest Systems

Probing into the Supramolecular Driving Force of an Amphiphilic β -Cyclodextrin Dimer in Various Solvents: Host–Guest Recognition or Hydrophilic–Hydrophobic Interaction?

Yang Bai, Xiao-dong Fan, Hao Yao, Zhen Yang, Ting-ting Liu, Hai-tao Zhang, Wan-bin Zhang, and Wei Tian
[Northwestern Polytechnical University]

J. Phys. Chem. B., **119**, 11893–11899, 2015.

Tuning of the morphology and size of supramolecular self-assemblies is of theoretical and practical significance. To date, supramolecular driving forces in different solvents remain unclear. In this study, we first synthesized an amphiphilic β -cyclodextrin (β -CD) dimer that consists of one hydrophobic ibuprofen (Ibu) and two hydrophilic β -CD moieties (i.e., Ibu-CD₂). Ibu-CD₂ possesses double supramolecular driving forces, namely, the host–guest recognition and hydrophilic–hydrophobic interaction.

1.2. Biopolymers

Bioinformatics and Cheminformatics

iFoldRNA v2: folding RNA with constraints

Andrey Krokhotin, Kevin Houlihan, and Nikolay V. Dokholyan [University of North Carolina, Chapel Hill]

Bioinformatics. **31**, 2891–2893, 2015.

A key to understanding RNA function is to uncover its complex 3D structure. Experimental methods used for determining RNA 3D structures are technologically challenging and laborious, which makes the development of computational prediction methods of substantial interest. Previously, we developed the iFoldRNA server that allows accurate prediction of short (<50 nt) tertiary RNA structures starting from primary sequences. Here, we present a new version of the iFoldRNA server that permits the prediction of tertiary structure of RNAs as long as a few hundred nucleotides.

PDBest: a user–friendly platform for manipulating and enhancing protein structures

Wellisson R. S. Gonçalves, Valdete M. Gonçalves-Almeida, Aleksander L. Arruda, Wagner Meira, Jr., Carlos H. da Silveira, Douglas E. V. Pires [Universidade Federal de Minas Gerais, Brazil], and Raquel C. de Melo-Minardi

Bioinformatics. **31**, 2894–2896, 2015.

PDBest (PDB Enhanced Structures Toolkit) is a user-friendly, freely available platform for acquiring, manipulating and normalizing protein structures in a high-throughput and seamless fashion. With an intuitive graphical interface it allows users with no programming background to download and manipulate their files. The platform also exports protocols, enabling users to easily share PDB searching and filtering criteria, enhancing analysis reproducibility.

Bioinformatics and Cheminformatics (Cont'd)

MemGen: a general web server for the setup of lipid membrane simulation systems

Christopher J. Knight and Jochen S. Hub [Georg-August-University Göttingen]

Bioinformatics. **31**, 2897-2899, 2015.

Molecular dynamics simulations provide atomic insight into the physicochemical characteristics of lipid membranes and hence, a wide range of force field families capable of modelling various lipid types have been developed in recent years. We present a new web service called MemGen that is capable of setting up simulation systems of heterogeneous lipid membranes. MemGen is not restricted to certain lipid force fields or lipid types, but instead builds membranes from uploaded structure files which may contain any kind of amphiphilic molecule. MemGen works with any all-atom or united-atom lipid representation.

MDN: A Web Portal for Network Analysis of Molecular Dynamics Simulations

Andre A.S.T. Ribeiro, Vanessa Ortiz [Columbia University, New York]

Biophysical Journal. **109**, 1110-1116, 2015.

We introduce a web portal that employs network theory for the analysis of trajectories from molecular dynamics simulations. Users can create protein energy networks following methodology previously introduced by our group, and can identify residues that are important for signal propagation, as well as measure the efficiency of signal propagation by calculating the network coupling. This tool, called MDN, was used to characterize signal propagation in *Escherichia coli* heat-shock protein 70-kDa.

Best bang for your buck: GPU nodes for GROMACS biomolecular simulations

Carsten Kutzner [Max Planck Institute for Biophysical Chemistry, Göttingen], Szilárd Páll, Martin Fechner, Ansgar Esztermann, Bert L. de Groot and Helmut Grubmüller

J. Comp. Chem., **36**, 1990–2008, 2015.

The molecular dynamics simulation package GROMACS runs efficiently on a wide variety of hardware from commodity workstations to high performance computing clusters. Hardware features are well-exploited with a combination of single instruction multiple data, multithreading, and message passing interface (MPI)-based single program multiple data/multiple program multiple data parallelism while graphics processing units (GPUs) can be used as accelerators to compute interactions off-loaded from the CPU. Here, we evaluate which hardware produces trajectories with GROMACS 4.6 or 5.0 in the most economical way.

LiSiCA: A Software for Ligand-Based Virtual Screening and Its Application for the Discovery of Butyrylcholinesterase Inhibitors

Samo Lešnik, Tanja Štular, Boris Brus, Damijan Knez, Stanislav Gobec, Dušanka Janežič [University of Primorska, Glagoljaška 8], and Janez Konc

J.Chem. Infor. and Mod. **55**, 1521–1528, 2015.

We developed LiSiCA (ligand similarity using clique algorithm)—ligand-based virtual screening software that uses a fast maximum clique algorithm to find two- and three-dimensional similarities between pairs of molecules and applied it to the discovery of novel potent butyrylcholinesterase inhibitors. LiSiCA, which runs in parallel on multiple processor cores, was successfully tested on the Database of Useful Decoys—Enhanced, to evaluate its ability to discriminate active molecules from decoys. We then applied LiSiCA for the discovery of novel inhibitors of human butyrylcholinesterase, a promising anti-Alzheimer target, using a known inhibitor as the reference compound.

Bioinformatics and Cheminformatics (Cont'd)

Discriminative Chemical Patterns: Automatic and Interactive Design

Stefan Bietz, Karen T. Schomburg, Matthias Hilbig, and Matthias Rarey [University of Hamburg, Bundesstrasse 43]

J.Chem. Infor. and Mod. **55**, 1535–1546, 2015.

The classification of molecules with respect to their inhibiting, activating, or toxicological potential constitutes a central aspect in the field of cheminformatics. Often, a discriminative feature is needed to distinguish two different molecule sets. Besides physicochemical properties, substructures and chemical patterns belong to the descriptors most frequently applied for this purpose. As a commonly used example of this descriptor class, SMARTS strings represent a powerful concept for the representation and processing of abstract chemical patterns. Here, we introduce SMARTSminer, a new algorithm for the automatic derivation of discriminative SMARTS patterns from preclassified molecule sets.

CHARMM-GUI Martini Maker for Coarse-Grained Simulations with the Martini Force Field

Yifei Qi, Helgi I. Ingólfsson, Xi Cheng, Jumin Lee, Siewert J. Marrink, and Wonpil Im [The University of Kansas, 2030 Becker Drive]

J. Chem. Theor. and Comp. **11**, 4486–4494, 2015.

Coarse-grained simulations are widely used to study large biological systems. Nonetheless, building such simulation systems becomes nontrivial, especially when membranes with various lipid types are involved. Taking advantage of the frameworks in all-atom CHARMM-GUI modules, we have developed CHARMM-GUI Martini Maker for building solution, micelle, bilayer, and vesicle systems as well as systems with randomly distributed lipids using the Martini force field. Martini Maker supports 82 lipid types and different flavors of the Martini force field, including polar and nonpolar Martini, Dry Martini, and ElNeDyn (an elastic network model for proteins).

Protein Conformational Analysis

The Role of Conformational Dynamics and Allostery in the Disease Development of Human Ferritin

Avishek Kumar, Tyler J. Glembo, S. Banu Ozkan [Arizona State University, Tempe]

Biophysical Journal. **109**, 1273–1281, 2015.

Determining the three-dimensional structure of myoglobin, the first solved structure of a protein, fundamentally changed the way protein function was understood. Even more revolutionary was the information that came afterward: protein dynamics play a critical role in biological functions. We recently analyzed the evolution of different protein families including green fluorescent proteins (GFPs), β -lactamase inhibitors, and nuclear receptors, and we observed that the alteration of conformational dynamics through allosteric regulation leads to functional changes. In this study, we analyzed the conformational dynamics of the wild-type light chain subunit of human ferritin protein along with the neutral and disease forms.

Protein Conformational Analysis (Cont'd)

A user-friendly web portal for analyzing conformational changes in structures of *Mycobacterium tuberculosis*

Sameer Hassan, Manonanthini Thangam, Praveen Vasudevan, G. Ramesh Kumar, Rahul Unni, P. K. Gayathri Devi, Luke Elizabeth Hanna [National Institute for Research in Tuberculosis, Chetpet]

J. Mol.Mod., **21**, 252, 2015.

Initiation of the Tuberculosis Structural Consortium has resulted in the expansion of the Mycobacterium tuberculosis (MTB) protein structural database. Currently, 969 experimentally solved structures are available for 354 MTB proteins. This includes multiple crystal structures for a given protein under different functional conditions, such as the presence of different ligands or mutations. In depth analysis of the multiple structures reveal that subtle differences exist in conformations of a given protein under varied conditions. Here, we introduce a web portal (<http://bmi.icmr.org.in/mtbsd/torsion.php>) that we developed to provide comparative data on the ensemble of available structures of MTB proteins.

ASCONA: Rapid Detection and Alignment of Protein Binding Site Conformations

Stefan Bietz and Matthias Rarey [University of Hamburg]

J.Chem. Infor. and Mod. **55**, 1747–1756, 2015.

The usage of conformational ensembles constitutes a widespread technique for the consideration of protein flexibility in computational biology. When experimental structures are applied for this purpose, alignment techniques are usually required in dealing with structural deviations and annotation inconsistencies. Moreover, many application scenarios focus on protein ligand binding sites. Here, we introduce our new alignment algorithm ASCONA that has been specially geared to the problem of aligning multiple conformations of sequentially similar binding sites.

Free Energy Landscapes of Alanine Oligopeptides in Rigid-Body and Hybrid Water Models

Divya Nayar and Charusita Chakravarty [Indian Institute of Technology-Delhi]

J. Phys. Chem. B., **119**, 11106–11120, 2015.

Replica exchange molecular dynamics is used to study the effect of different rigid-body (mTIP3P, TIP4P, SPC/E) and hybrid (H1.56, H3.00) water models on the conformational free energy landscape of the alanine oligopeptides (acAnme and acA₅nme), in conjunction with the CHARMM22 force field. The free energy landscape is mapped out as a function of the Ramachandran angles. In addition, various secondary structure metrics, solvation shell properties, and the number of peptide-solvent hydrogen bonds are monitored. Alanine dipeptide is found to have similar free energy landscapes in different solvent models, an insensitivity which may be due to the absence of possibilities for forming i –($i + 4$) or i –($i + 3$) intrapeptide hydrogen bonds.

Protein Conformational Analysis (Cont'd)

Direct Measurement of the Nanomechanical Stability of a Redox Protein Active Site and Its Dependence upon Metal Binding

Marina I. Giannotti, Israel Cabeza de Vaca, Juan M. Artés, Fausto Sanz, Victor Guallar, and Pau Gorostiza [Biomaterials and Nanomedicine (CIBER-BBN)]

J. Phys. Chem. B., **119**, 12050–12058, 2015.

The structural basis of the low reorganization energy of cupredoxins has long been debated. These proteins reconcile a conformationally heterogeneous and exposed metal-chelating site with the highly rigid copper center required for efficient electron transfer. Here we combine single-molecule mechanical unfolding experiments with statistical analysis and computer simulations to show that the metal-binding region of apo-azurin is mechanically flexible and that high mechanical stability is imparted by copper binding.

Fast gap-free enumeration of conformations and sequences for protein design

Kyle E. Roberts, Pablo Gainza, Mark A. Hallen and Bruce R. Donald [Duke University]

Proteins: Stru. Fun. & Bioinf., **83**, 1859–1877, 2015.

Despite significant successes in structure-based computational protein design in recent years, protein design algorithms must be improved to increase the biological accuracy of new designs. Protein design algorithms search through an exponential number of protein conformations, protein ensembles, and amino acid sequences in an attempt to find globally optimal structures with a desired biological function. To improve the biological accuracy of protein designs, it is necessary to increase both the amount of protein flexibility allowed during the search and the overall size of the design, while guaranteeing that the lowest-energy structures and sequences are found.

Protein Structure Prediction

Selective refinement and selection of near-native models in protein structure prediction

Jiong Zhang, Bogdan Barz, Jingfen Zhang, Dong Xu and Ioan Kosztin [University of Missouri, Columbia]

Proteins: Stru. Fun. & Bioinf., **83**, 1823–1835, 2015.

In recent years in silico protein structure prediction reached a level where fully automated servers can generate large pools of near-native structures. However, the identification and further refinement of the best structures from the pool of models remain problematic. To address these issues, we have developed (i) a target-specific selective refinement (SR) protocol; and (ii) molecular dynamics (MD) simulation based ranking (SMDR) method. In SR the all-atom refinement of structures is accomplished via the Rosetta Relax protocol, subject to specific constraints determined by the size and complexity of the target.

Protein Dynamics

Synaptobrevin Transmembrane Domain Dimerization Studied by Multiscale Molecular Dynamics Simulations

Jing Han, Kristyna Pluhackova, Tsjerk A. Wassenaar, Rainer A. Böckmann [Friedrich-Alexander Universität Erlangen-Nürnberg]

Biophysical Journal. **109**, 760-771, 2015.

Synaptic vesicle fusion requires assembly of the SNARE complex composed of SNAP-25, syntaxin-1, and synaptobrevin-2 (sybII) proteins. The SNARE proteins found in vesicle membranes have previously been shown to dimerize via transmembrane (TM) domain interactions. While syntaxin homodimerization is supposed to promote the transition from hemifusion to complete fusion, the role of synaptobrevin's TM domain association in the fusion process remains poorly understood. Here, we combined coarse-grained and atomistic simulations to model the homodimerization of the sybII transmembrane domain and of selected TM mutants.

AquaBridge: A novel method for systematic search of structural water molecules within the protein active sites

Arina Afanasyeva [St. Petersburg State Polytechnical University], Sergey Izmailov, Michel Grigoriev and Michael Petukhov

J. Comp. Chem., **36**, 1973–1977, 2015.

We have developed a novel method for calculation of the water bridges that can be formed in the active sites of proteins in the absence or in the presence of small-molecule ligands. We tested its efficiency on a representative set of human ATP-binding proteins, and show that the docking accuracy of ligands can be substantially improved when water bridges are included in the modeling of protein–ligand interactions. Our analysis of binding pocket hydration can be a useful addition to the in silico approaches of Drug Design.

Enhanced stability of the model mini-protein in amino acid ionic liquids and their aqueous solutions

Guillaume Chevrot, Eudes Eterno Fileti [Universidade Federal de São Paulo] and Vitaly V. Chaban

J. Comp. Chem., **36**, 2044–2051, 2015.

Using molecular dynamics simulations, the structure of model mini-protein was thoroughly characterized in the imidazolium-based amino acid ionic liquids and their aqueous solutions. Complete substitution of water by organic cations and anions further results in hindered conformational flexibility of the mini-protein. This observation suggests that amino acid-based ionic liquids are able to defend proteins from thermally induced denaturation. We show by means of radial distributions that the mini-protein is efficiently solvated by both solvents due to a good mutual miscibility.

Polymorphic Associations and Structures of the Cross-Seeding of A β _{1–42} and hIAPP_{1–37} Polypeptides

Mingzhen Zhang, Rundong Hu, Hong Chen, Xiong Gong, Feimeng Zhou, Li Zhang, and Jie Zheng [The University of Akron, Akron]

J.Chem. Infor. and Mod. **55**, 1628–1639, 2015.

Emerging evidence have shown that the patients with Alzheimer's disease (AD) often have a higher risk of later developing type II diabetes (T2D), and vice versa, suggesting a potential pathological link between AD and T2D. Amyloid- β (A β) and human islet amyloid polypeptide (hIAPP) are the principle causative components responsible for the pathologies of AD and T2D, respectively. Herein, we systematically modeled and simulated the cross-sequence aggregation process, molecular interactions, and polymorphic structures of full-length A β and hIAPP peptides using a combination of coarse-grained (CG) replica-exchange molecular dynamics (REMD) and all-atom molecular dynamics (MD) simulations.

Protein Dynamics (Cont'd)

Toward Modular Analysis of Supramolecular Protein Assemblies

Jaehoon Kim, Jin-Gyun Kim, Giseok Yun, Phill-Seung Lee, and Do-Nyun Kim [Seoul National University, Gwanak-ro 1]

J. Chem. Theor. and Comp., **11**, 4260–4272, 2015.

Despite recent advances in molecular simulation technologies, analysis of high-molecular-weight structures is still challenging. Here, we propose an automated model reduction procedure aiming to enable modular analysis of these structures. It employs a component mode synthesis for the reduction of finite element protein models. Reduced models may consist of real biological subunits or artificial partitions whose dynamics is described using the degrees of freedom at the substructural interfaces and a small set of dominant vibrational modes only.

Local Structure and Dynamics of Hydration Water in Intrinsically Disordered Proteins

Pooja Rani and Parbati Biswas [University of Delhi, Delhi]

J. Phys. Chem. B., **119**, 10858–10867, 2015.

Hydration water around protein surface plays a key role in structure, folding and dynamics of proteins. Intrinsically disordered proteins lack secondary and/or tertiary structure in their native state. Thus, characterizing the local structure and dynamics of hydration water around disordered proteins is challenging for both experimentalists and theoreticians. The local structure, orientation and dynamics of hydration water in the vicinity of intrinsically disordered proteins is investigated through molecular dynamics simulations.

Investigating the Counteracting Effect of Trehalose on Urea-Induced Protein Denaturation Using Molecular Dynamics Simulation

Subrata Paul and Sandip Paul [Indian Institute of Technology, Guwahati]

J. Phys. Chem. B., **119**, 10975–10988, 2015.

Molecular dynamics simulations are performed to investigate the counteracting effect of trehalose against urea-induced denaturation of S-peptide analogue. The calculations of C_α root-mean-square deviation, radius of gyration, and solvent-accessible surface area reveal that the peptide loses its native structure in aqueous 8 M urea solution at 310 K and that this unfolding process is prevented in the presence of trehalose. Interestingly, the native structure of the peptide in ternary mixed urea/trehalose solution is similar to that in the pure water system.

Will It Be Beneficial To Simulate the Antifreeze Proteins at Ice Freezing Condition or at Lower Temperature?

Rajiv K. Kar and Anirban Bhunia [Bose Institute]

J. Phys. Chem. B., **119**, 11485–11495, 2015.

Antifreeze proteins (AFPs) enable the polar living species to survive subzero temperature conditions through effective lowering of the freezing point of body fluids. At the molecular level, AFPs directly interact with the growing seeds of ice crystals to inhibit their formation. To understand the structural and dynamic aspects of this interaction at the atomistic level, molecular dynamics (MD) simulations were carried out on several type I AFPs at multiple temperatures, including the physiologically relevant temperature of 273 K, a lower temperature of 227 K, and the conventional 300 K.

Protein Dynamics (Cont'd)

Ab Initio Molecular Dynamics Simulations of Amino Acids in Aqueous Solutions: Estimating pK_a Values from Metadynamics Sampling

Anil Kumar Tummanapelli and Sukumaran Vasudevan
[Indian Institute of Science, Bangalore]

J. Phys. Chem. B., **119**, 12249–12255, 2015.

Changes in the protonation and deprotonation of amino acid residues in proteins play a key role in many biological processes and pathways. Here, we report calculations of the free-energy profile for the protonation–deprotonation reaction of the 20 canonical α amino acids in aqueous solutions using ab initio Car–Parrinello molecular dynamics simulations coupled with metadynamics sampling. We show here that the calculated change in free energy of the dissociation reaction provides estimates of the multiple pK_a values of the amino acids that are in good agreement with experiment.

Investigation of the molecular similarity in closely related protein systems: The PrP case study

Loriano Storchi, Roberto Paciotti, Nazzareno Re and Alessandro Marrone [Università “G D'annunzio” Di Chieti-Pescara]

Proteins: Stru. Fun. & Bioinf., **83**, 1751–1765, 2015.

The amyloid conversion is a massive detrimental modification affecting several proteins upon specific physical or chemical stimuli characterizing a plethora of diseases. In many cases, the amyloidogenic stimuli induce specific structural features to the protein conferring the propensity to misfold and form amyloid deposits. The investigation of mutants, structurally similar to their native isoform but inherently prone to amyloid conversion, may be a viable strategy to elucidate the structural features connected with amyloidogenesis. In this article, we present a computational protocol based on the combination of molecular dynamics (MD) and grid-based approaches suited for the pairwise comparison of closely related protein structures.

Free Energy Calculations

Qgui: A high-throughput interface for automated setup and analysis of free energy calculations and empirical valence bond simulations in biological systems

Geir Villy Isaksen, Tor Arne Heim Andberg, Johan Åqvist, Bjørn Olav Brandsdal [University of Tromsø]

J. Mol. Graph. and Mod., **60**, 15–23, 2015.

Structural information and activity data has increased rapidly for many protein targets during the last decades. In this paper, we present a high-throughput interface (Qgui) for automated free energy and empirical valence bond (EVB) calculations that use molecular dynamics (MD) simulations for conformational sampling. Applications to ligand binding using both the linear interaction energy (LIE) method and the free energy perturbation (FEP) technique are given using the estrogen receptor (ER α) as a model system.

Evaluating Free Energies of Binding and Conservation of Crystallographic Waters Using SZMAP

Alexander S. Bayden, Demetri T. Moustakas, Diane Joseph-McCarthy, and Michelle L. Lamb [AstraZeneca R&D Boston]

J. Chem. Infor. and Mod., **55**, 1552–1565, 2015.

The SZMAP method computes binding free energies and the corresponding thermodynamic components for water molecules in the binding site of a protein structure [SZMAP, 1.0.0; OpenEye Scientific Software Inc.: Santa Fe, NM, USA, 2011]. In this work, the ability of SZMAP to predict water structure and thermodynamic stability is examined for the X-ray crystal structures of a series of protein–ligand complexes. SZMAP results correlate with higher-level replica exchange thermodynamic integration double decoupling calculations of the absolute free energy of bound waters in the test set complexes.

Free Energy Calculations (Cont'd)

Quantum Corrections to the Free Energy Difference between Peptides and Proteins Conformers

Marco Cecchini [Université de Strasbourg]

J. Chem. Theor. and Comp., **11**, 4011–4022, 2015.

The calculation of the free energy of conformation is key in understanding the function of biomolecules and has attracted significant interest in recent years. Most current computational approaches evaluate the difference in conformational free energy in the classical limit based on the common “dogma” that only the lowest-frequency modes make a significant contribution to it, i.e. they assume that quantum mechanical corrections are negligible. Here, I show for three biomolecular systems described in the rigid-rotor, harmonic-oscillator approximation that the zero-point energy contribution, although small, is not negligible even at room temperature.

Ligand Binding/Docking

Studying the binding interactions of allosteric agonists and antagonists of the CXCR4 receptor

Jesús M. Planesas, Violeta I. Pérez-Nueno, José I. Borrell, Jordi Teixidó [Universitat Ramon Llull, Barcelona]

J. Mol.Graph. and Mod., **60**, 1-14 , 2015.

Several examples of allosteric modulators of GPCRs have been reported recently in the literature, but understanding their molecular mechanism presents a new challenge for medicinal chemistry. For the specific case of the cellular receptor CXCR4, it is known that pepducins (lipidated fragments of intracellular GPCR loops) such as ATI-2341 modulate CXCR4 activity agonistically via an allosteric mechanism. Moreover, there are also examples of small organic molecules such as AMD11070 and GSK812397 which may also act as allosteric antagonists. Here, we attempt to answer this question by analysing the binding interactions between the CXCR4 receptor and the above-mentioned allosteric modulators.

Higher-Affinity Agonists of 5-HT_{1A}R Discovered through Tuning the Binding-Site Flexibility

Peng Lian, LinLang Li, Chuanrong Geng, Xuechu Zhen [Soochow University, Suzhou], and Wei Fu

J.Chem. Infor. and Mod. **55**, 1616–1627, 2015.

Discovery of high-affinity and high-selectivity agonists of 5-HT_{1A}R has become very attractive due to their potential therapeutic effects on multiple 5-HT_{1A}R-related psychological and neurological problems. On the basis of our previously designed lead compound FW01 ($K_i = 51.9$ nM, denoted as 9a in the present study), we performed large-scale molecular dynamics simulations and molecular docking operations on 5-HT_{1A}R-9a binding. We found the flip-packing events for the headgroup of 9a, and we also found that its tail group could bind flexibly at the agonist-binding site of 5-HT_{1A}R.

Ligand Binding / Docking (Cont'd)

High Resolution Prediction of Calcium-Binding Sites in 3D Protein Structures Using FEATURE

Weizhuang Zhou, Grace W. Tang, and Russ B. Altman
[Stanford University]

J.Chem. Infor. and Mod. **55**, 1663–1672, 2015.

Metal-binding proteins are ubiquitous in biological systems ranging from enzymes to cell surface receptors. Among the various biologically active metal ions, calcium plays a large role in regulating cellular and physiological changes. With the increasing number of high-quality crystal structures of proteins associated with their metal ion ligands, many groups have built models to identify Ca^{2+} sites in proteins, utilizing information such as structure, geometry, or homology to do the inference. We present a FEATURE-based approach in building such a model and show that our model is able to discriminate between nonsites and calcium-binding sites with a very high precision of more than 98%.

Evidence for a Transient Additional Ligand Binding Site in the TAS2R46 Bitter Taste Receptor

Massimo Sandal, Maik Behrens, Anne Brockhoff, Francesco Musiani, Alejandro Giorgetti, Paolo Carloni [German Research School for Simulation Sciences], and Wolfgang Meyerhof

J. Chem. Theor. and Comp. **11**, 4439–4449, 2015.

Most human G protein coupled receptors (GPCRs) are activated by small molecules binding to their 7-transmembrane (7-TM) helix bundle. They belong to basally diverging branches: the 25 bitter taste 2 receptors and most members of the very large rhodopsin-like/class A GPCRs subfamily. Some members of the class A branch have been suggested to feature not only an orthosteric agonist-binding site but also a more extracellular or “vestibular” site, involved in the binding process. Here we use a hybrid molecular mechanics/coarse-grained (MM/CG) molecular dynamics approach on a widely studied bitter taste receptor (TAS2R46) receptor in complex with its agonist strychnine.

Resistance-Mutation (N31) Effects on Drug Orientation and Channel Hydration in Amantadine-Bound Influenza A M2

Mitchell L. Gleed, Harris Ioannidis, Antonios Kolocouris, and David D. Busath [Brigham Young University, Provo]

J. Phys. Chem. B., **119**, 11548–11559, 2015.

The mechanism of amantadine binding to the S31 variant of the M2 protein of Influenza A is well understood, but the reasons behind N31 M2 amantadine insensitivity remain under investigation. Many molecular dynamics studies have evaluated the influence of amantadine position within the channel pore on its ability to inhibit proton conductance in M2, but little is known about the influence of amantadine rotational orientation. Replica-exchange umbrella sampling, steered, and classic molecular dynamics simulations were performed on amantadine in the solid-state NMR structure of S31 M2 and an N31 M2 homologue, both in the homotetramer configuration, to explore the effects of the position and tilt angle of amantadine on inhibition of the M2 channel.

Ligand Binding / Docking (Cont'd)

Investigation of the Binding Profiles of AZD2184 and Thioflavin T with Amyloid- β (1–42) Fibril by Molecular Docking and Molecular Dynamics Methods

Guanglin Kuang, N. Arul Murugan [KTH Royal Institute of Technology], Yaoquan Tu, Agneta Nordberg, and Hans Ågren

J. Phys. Chem. B., **119**, 11560–11567, 2015.

Detecting deposits of amyloid β fibrils in the brain is of paramount importance for an early diagnosis of Alzheimer's disease. A number of PET tracers have been developed for amyloid imaging, but many suffer from poor specificity and large signal to background ratio. Design of tracers with specificity and improved binding affinity requires knowledge about various potential binding sites in the amyloid β fibril available for the tracers and the nature of the local microenvironment of these sites. In this study we investigate the local structure of fibrils using two important probes, namely, thioflavin T (a fluorescent probe) and AZD2184 (a PET tracer).

Molecular Mechanisms of Alzheimer's Biomarker FDDNP Binding to A β Amyloid Fibril

Niyati D. Parikh and Dmitri K. Klimov [George Mason University, Manassas]

J. Phys. Chem. B., **119**, 11568–11580, 2015.

Using isobaric–isothermal replica exchange molecular dynamics and the all-atom explicit water model, we examined the binding of FDDNP biomarkers to the A β amyloid fibril fragment. Our results can be summarized as follows. First, FDDNP ligands bind with high affinity to the A β fibril, and the hydrophobic effect together with π -stacking interactions are the dominant factors governing FDDNP binding. In comparison, electrostatic interactions and hydrogen bonding play a minor role. Second, our simulations reveal a strong tendency of bound FDDNP molecules for self-aggregation.

Molecular dynamics simulations indicate that tyrosineB10 limits motions of distal histidine to regulate CO binding in soybean leghemoglobin

Smriti Sharma, Amit Kumar, Suman Kundu [University of Delhi South Campus, New Delhi] and Pradipta Bandyopadhyay

Proteins: Stru. Fun. & Bioinf., **83**, 1836–1848, 2015.

Myoglobin (Mb) uses strong electrostatic interaction in its distal heme pocket to regulate ligand binding. The mechanism of regulation of ligand binding in soybean leghemoglobin a (Lba) has been enigmatic and more so due to the absence of gaseous ligand bound atomic resolution three-dimensional structure of the plant globin. While the 20-fold higher oxygen affinity of Lba compared with Mb is required for its dual physiological function, the mechanism by which this high affinity is achieved is only emerging. Extensive mutational analysis combined with kinetic and CO-FT-IR spectroscopic investigation led to the hypothesis that Lba depended on weakened electrostatic interaction between distal HisE7 and bound ligand achieved by invoking B10Tyr.

Enzyme Catalysis

Comparative molecular field analysis and molecular dynamics studies of α/β hydrolase domain containing 6 (ABHD6) inhibitors

Agnieszka A. Kaczor [Medical University of Lublin], Katarzyna M. Targowska-Duda, Jayendra Z. Patel, Teija Parkkari, Yahaya Adams, Tapio J. Nevalainen, Antti Poso

J. Mol.Mod., **21**, 250, 2015.

The endocannabinoid system remains an attractive molecular target for pharmacological intervention due to its roles in the central nervous system in learning, thinking, emotional function, regulation of food intake or pain sensation, as well as in the peripheral nervous system, where it modulates the action of cardiovascular, immune, metabolic or reproductive function. α/β hydrolase domain containing 6 (ABHD6)—an enzyme forming part of the endocannabinoid system—is a newly discovered post-genomic protein acting as a 2-AG (2-arachidonoylglycerol) serine hydrolase. We have recently reported a series of 1,2,5-thiadiazole carbamates as potent and selective ABHD6 inhibitors. Here, we present comparative molecular field analysis (CoMFA) and molecular dynamics studies of these compounds.

Molecular Dynamics Simulations and Structural Network Analysis of c-Abl and c-Src Kinase Core Proteins: Capturing Allosteric Mechanisms and Communication Pathways from Residue Centrality

Amanda Tse and Gennady M. Verkhivker [Chapman University, One University Drive]

J.Chem. Infor. and Mod. **55**, 1645–1662, 2015.

The Abl and Src tyrosine kinases play a fundamental regulatory role in orchestrating functional processes in cellular networks and represent an important class of therapeutic targets. In this work, we combine biophysical simulations with computational modeling of the residue interaction networks to characterize allosteric mechanisms of kinase regulation and gain insight into differential sensitivity of c-Abl and c-Src kinases to specific drug binding. Using these approaches, we examine dynamics of cooperative rearrangements in the residue interaction networks and elucidate the structural role of regulatory residues responsible for modulation of kinase activity.

Determination of the Reaction Coordinate for a Key Conformational Fluctuation in Human Carbonic Anhydrase II

Sanjib Paul and Srabani Taraphder [Indian Institute of Technology, Kharagpur]

J. Phys. Chem. B., **119**, 11403–11415, 2015.

During the reversible hydration of carbon dioxide into bicarbonate by the enzyme human carbonic anhydrase II, the rate-determining step of proton transfer across the active site has been suggested to involve side chain rotation of the residue His-64 shuttling an excess proton in and out of the active site. In the present article, we have determined the reaction coordinate for this catalytically important conformational transition starting from a set of 32 order parameters (or candidate collective variables).

Enzyme Catalysis (Cont'd)

Probing the Catalytic Mechanism Involved in the Isocitrate Lyase Superfamily: Hybrid Quantum Mechanical/Molecular Mechanical Calculations on 2,3-Dimethylmalate Lyase

Nathjanaan Jongkon, Warot Chotapatiwetchkul, and M. Paul Gleeson [Kasetsart University]

J. Phys. Chem. B., **119**, 11473–11484, 2015.

The isocitrate lyase (ICL) superfamily catalyzes the cleavage of the C(2)–C(3) bond of various α -hydroxy acid substrates. Members of the family are found in bacteria, fungi, and plants and include ICL itself, oxaloacetate hydrolase (OAH), 2-methylisocitrate lyase (MICL), and (2R,3S)-dimethylmalate lyase (DMML) among others. ICL and related targets have been the focus of recent studies to treat bacterial and fungal infections, including tuberculosis. The catalytic process by which this family achieves C(2)–C(3) bond breaking is still not clear. Extensive structural studies have been performed on this family, leading to a number of plausible proposals for the catalytic mechanism.

Enzyme Selectivity of HIV Reverse Transcriptase: Conformations, Ligands, and Free Energy Partition

Serdal Kirmizialtin, Kenneth A. Johnson, and Ron Elber [University of Texas at Austin]

J. Phys. Chem. B., **119**, 11513–11526, 2015.

Atomically detailed simulations of HIV RT are performed to investigate the contributions of the conformational transition to the overall rate and specificity of enzyme catalysis. A number of different scenarios are considered within Milestoning theory to provide a more complete picture of the process of opening and closing the enzyme. We consider the open to closed transition in the absence of and with the correct and incorrect substrates. We also consider the free energy profile and the kinetics of the conformational change after the chemistry step in which a new base was added to the DNA, but the DNA was not yet displaced.

Protein-Protein Interactions

AlphaSpace: Fragment-Centric Topographical Mapping To Target Protein–Protein Interaction Interfaces

David Rooklin, Cheng Wang, Joseph Katigbak, Paramjit S. Arora, and Yingkai Zhang [New York University, New York]

J. Chem. Infor. and Mod. **55**, 1585–1599, 2015.

Inhibition of protein–protein interactions (PPIs) is emerging as a promising therapeutic strategy despite the difficulty in targeting such interfaces with drug-like small molecules. PPIs generally feature large and flat binding surfaces as compared to typical drug targets. These features pose a challenge for structural characterization of the surface using geometry-based pocket-detection methods. Here, we introduce AlphaSpace, a computational analysis tool designed for fragment-centric topographical mapping (FCTM) of PPI interfaces.

Computing Protein–Protein Association Affinity with Hybrid Steered Molecular Dynamics

Roberto A. Rodriguez, Lili Yu, and Liao Y. Chen [University of Texas at San Antonio]

J. Chem. Theor. and Comp., **11**, 4427–4438, 2015.

Computing protein–protein association affinities is one of the fundamental challenges in computational biophysics/biochemistry. The overwhelming amount of statistics in the phase space of very high dimensions cannot be sufficiently sampled even with today's high-performance computing power. In this article, we extend a potential of mean force (PMF)-based approach, the hybrid steered molecular dynamics (hSMD) approach we developed for ligand–protein binding, to protein–protein association problems.

Membrane Proteins and Lipid Peptide Interactions

Thermodynamics of Micelle Formation and Membrane Fusion Modulate Antimicrobial Lipopeptide Activity

Dejun Lin, Alan Grossfield [University of Rochester Medical Center]

Biophysical Journal. **109**, 750-759, 2015.

Antimicrobial lipopeptides (AMLPs) are antimicrobial drug candidates that preferentially target microbial membranes. One class of AMLPs, composed of cationic tetrapeptides attached to an acyl chain, have minimal inhibitory concentrations in the micromolar range against a range of bacteria and fungi. Previously, we used coarse-grained molecular dynamics simulations and free energy methods to study the thermodynamics of their interaction with membranes in their monomeric state. Here, we extended the study to the biologically relevant micellar state, using, to our knowledge, a novel reaction coordinate based on hydrophobic contacts.

Molecular Basis of the Membrane Interaction of the $\beta 2e$ Subunit of Voltage-Gated Ca^{2+} Channels

Dong-Il Kim, Mooseok Kang, Sangyeol Kim, Juhwan Lee, Yongsoo Park, Iksoo Chang, Byung-Chang Suh [Daegu Gyeongbuk Institute of Science and Technology]

Biophysical Journal. **109**, 922-935, 2015.

The auxiliary β subunit plays an important role in the regulation of voltage-gated calcium (Ca_v) channels. Recently, it was revealed that $\beta 2e$ associates with the plasma membrane through an electrostatic interaction between N-terminal basic residues and anionic phospholipids. However, a molecular-level understanding of β -subunit membrane recruitment in structural detail has remained elusive. In this study, using a combination of site-directed mutagenesis, liposome-binding assays, and multiscale molecular-dynamics (MD) simulation, we developed a physical model of how the $\beta 2e$ subunit is recruited electrostatically to the plasma membrane.

Modulating bilayer mechanical properties to promote the coupled folding and insertion of an integral membrane protein

Michaela Herrmann, Bartholomäus Danielczak, Martin Textor, Jessica Klement, Sandro Keller [University of Kaiserslautern]

Eur.Biophys., **44**, 503-512, 2015.

Bilayer mechanical properties are not only of crucial importance to the mechanism of action of mechanosensation in lipid membranes but also affect preparative laboratory tasks such as membrane-protein refolding. We report this for coupled refolding and bilayer insertion of outer membrane phospholipase A (OmpLA), an integral membrane enzyme that catalyses the hydrolytic cleavage of glycerophospholipids. OmpLA can be refolded into a variety of detergent micelles and unilamellar vesicles composed of short-chain phospholipids but, in the absence of chemical or molecular chaperones, not into thicker membranes.

Interaction of menthol with mixed-lipid bilayer of stratum corneum: A coarse-grained simulation study

Guang Wan, Xingxing Dai, Qianqian Yin, Xinyuan Shi, Yanjiang Qiao [Beijing University of Chinese Medicine]

J. Mol.Graph. and Mod., **60**, 98-107 , 2015.

Menthol is a widely used penetration enhancer in clinical medicine due to its high efficiency and relative safety. Although there are many studies focused on the penetration-enhancing activity of menthol, the details of molecular mechanism are rarely involved in the discussion. In this study, we present a series of coarse-grained molecular dynamics simulations to investigate the interaction of menthol with a mixed-lipid bilayer model consisting of ceramides, cholesterol and free fatty acids in a 2:2:1 molar ratio.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Structure-based virtual screening as a tool for the identification of novel inhibitors against *Mycobacterium tuberculosis* 3-dehydroquinate dehydratase

Guilherme O. Petersen, Shalini Saxena, Janupally Renuka, Vijay Soni, Perumal Yogeeswari, Diogenes S. Santos, Cristiano V. Bizarro [Pontifícia Universidade Católica do Rio Grande do Sul], Dharmarajan Sriram

J. Mol.Graph. and Mod., **60**, 124-131 , 2015.

3-Dehydroquinate dehydratase (DHQase), the third enzyme of the shikimate pathway, catalyzes the reversible reaction of 3-dehydroquinate into 3-dehydroshikimate. The aim of the present study was to identify new drug-like molecules as inhibitors for *Mycobacterium tuberculosis* DHQase employing structure-based pharmacophore modeling technique using an in house database consisting of about 2500 small molecules. Further the pharmacophore models were validated using enrichment calculations, and finally three models were employed for high-throughput virtual screening and docking to identify novel small molecules as DHQase inhibitors.

Effective virtual screening strategy focusing on the identification of novel Bruton's tyrosine kinase inhibitors

Jianhu Xiao, Shengping Zhang, Minghao Luo, Yi Zou, Yihua Zhang, Yisheng Lai [China Pharmaceutical University]

J. Mol.Graph. and Mod., **60**, 142-154, 2015.

Dysregulation of the B-cell receptor (BCR) signaling pathway plays a vital role in the pathogenesis and development of B-cell malignancies. Bruton's tyrosine kinase (BTK), a key component in the BCR signaling, has been validated as a valuable target for the treatment of B-cell malignancies. In an attempt to find novel and potent BTK inhibitors, both ligand- and structure-based pharmacophore models were generated using Discovery Studio 2.5 and Ligandscout 3.11 with the aim of screening the ChemBridge database.

Effects of imidazolium-based ionic surfactants on the size and dynamics of phosphatidylcholine bilayers with saturated and unsaturated chains

Hwankyu Lee [Dankook University, Yongin]

J. Mol.Graph. and Mod., **60**, 162-168, 2015.

Imidazolium-based ionic surfactants of different sizes were simulated with 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) bilayers. Regardless of the phospholipid type, larger surfactants at higher concentrations more significantly insert into the bilayer and increase the bilayer-surface size, in agreement with experiments and previous simulations. Insertion of surfactants only slightly decreases the bilayer thickness, as also observed in experiments.

Adaptable Lipid Matrix Promotes Protein–Protein Association in Membranes

Andrey S. Kuznetsov, Anton A. Polyansky, Markus Fleck, Pavel E. Volynsky, and Roman G. Efremov [Russian Academy of Sciences, Miklukho-Maklaya Str.]

J. Chem. Theor. and Comp., **11**, 4415–4426, 2015.

The cell membrane is “stuffed” with proteins, whose transmembrane (TM) helical domains spontaneously associate to form functionally active complexes. For a number of membrane receptors, a modulation of TM domains’ oligomerization has been shown to contribute to the development of severe pathological states, thus calling for detailed studies of the atomistic aspects of the process. Here, we assess the dimerization free energy of TM helices along with a careful consideration of the interplay between the structure and dynamics of protein and lipids using atomistic molecular dynamics simulations in the hydrated lipid bilayer for three different model systems – TM fragments of glycophorin A, polyalanine and polyleucine peptides.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Protein–Ligand Electrostatic Binding Free Energies from Explicit and Implicit Solvation

Saeed Izadi, Boris Aguilar, and Alexey V. Onufriev [Virginia Tech, Blacksburg]

J. Chem. Theor. and Comp, **11**, 4450–4459, 2015.

Accurate yet efficient computational models of solvent environment are central for most calculations that rely on atomistic modeling, such as prediction of protein–ligand binding affinities. In this study, we evaluate the accuracy of a recently developed generalized Born implicit solvent model, GBNSR6 (Aguilar et al. *J. Chem. Theory Comput.* 2010, 6, 3613–3639), in estimating the electrostatic solvation free energies (ΔG_{pol}) and binding free energies ($\Delta\Delta G_{\text{pol}}$) for small protein–ligand complexes. We also compare estimates based on three different explicit solvent models (TIP3P, TIP4PEw, and OPC). The two main findings are as follows.

Specific Ion Binding at Phospholipid Membrane Surfaces

Jing Yang, Carles Calero, Massimiliano Bonomi, and Jordi Martí [Technical University of Catalonia-Barcelona Tech]

J. Chem. Theor. and Comp, **11**, 4495–4499, 2015.

Metal cations are ubiquitous components in biological environments and play an important role in regulating cellular functions and membrane properties. By applying metadynamics simulations, we have performed systematic free energy calculations of Na^+ , K^+ , Ca^{2+} , and Mg^{2+} bound to phospholipid membrane surfaces for the first time. The free energy landscapes unveil specific binding behaviors of metal cations on phospholipid membranes. Na^+ and K^+ are more likely to stay in the aqueous solution and can bind easily to a few lipid oxygens by overcoming low free energy barriers. Ca^{2+} is most stable when it is bound to four lipid oxygens of the membrane rather than being hydrated in the aqueous solution.

Molecular Dynamics Simulation Study of Skin Lipids: Effects of the Molar Ratio of Individual Components over a Wide Temperature Range

Rakesh Gupta and Beena Rai [Tata Consultancy Services]

J. Phys. Chem. B., **119**, 11643–11655, 2015.

Atomistic molecular dynamics (MD) simulations were employed to systematically investigate the effects of the molar ratio of the individual components cholesterol (CHOL), free fatty acid (FFA), and ceramides (CER) on the properties of the skin lipid bilayer over a wide temperature range (300–400 K). Several independent simulations were performed for bilayers comprised of only CER, CHOL, or FFA molecules as well as those made up of a mixture of CER:CHOL:FFA molecules in different molar ratios. It was found that CHOL increases the stability of the bilayer, since the mixed (CER:CHOL:FFA) 1:1:0, 1:1:1, and 2:2:1 bilayers remained stable until 400 K while the pure ceramide bilayer disintegrated around ~390 K.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Polysaccharide–Protein Complexes in a Coarse-Grained Model

Adolfo B. Poma [Polish Academy of Sciences, Aleja Lotników], Mateusz Chwastyk, and Marek Cieplak

J. Phys. Chem. B., **119**, 12028–12041, 2015.

We construct two variants of coarse-grained models of three hexaoses: one based on the centers of mass of the monomers and the other associated with the C4 atoms. The latter is found to be better defined and more suitable for studying interactions with proteins described within α -C based models. We determine the corresponding effective stiffness constants through all-atom simulations and two statistical methods. One method is the Boltzmann inversion (BI) and the other, named energy-based (EB), involves direct monitoring of energies as a function of the variables that define the stiffness potentials. The two methods are generally consistent in their account of the stiffness.

Microsecond Simulations of the Diphtheria Toxin Translocation Domain in Association with Anionic Lipid Bilayers

Jose C. Flores-Canales and Maria Kurnikova [Carnegie Mellon University, Pittsburgh]

J. Phys. Chem. B., **119**, 12074–12085, 2015.

Diphtheria toxin translocation (T) domain undergoes conformational changes in acidic solution and associates with the lipid membranes, followed by refolding and transmembrane insertion of two nonpolar helices. This process is an essential step in delivery of the toxic catalytic domain of the diphtheria toxin to the infected cell, yet its molecular determinants are poorly characterized and understood. Therefore, an atomistic model of the T-domain–membrane interaction is needed to help characterize factors responsible for such association. In this work, we present atomistic model structures of T-domain membrane-bound conformations and investigate structural factors responsible for T-domain affinity with the lipid bilayer in acidic solution using all-atom molecular dynamics (MD) simulations.

Protein Folding

An Analysis of Biomolecular Force Fields for Simulations of Polyglutamine in Solution

Aaron M. Fluit, Juan J. de Pablo [University of Chicago, Chicago]

Biophysical Journal. **109**, 1009-1018, 2015.

Polyglutamine (polyQ) peptides are a useful model system for biophysical studies of protein folding and aggregation, both for their intriguing aggregation properties and their own relevance to human disease. The genetic expansion of a polyQ tract triggers the formation of amyloid aggregates associated with nine neurodegenerative diseases. Several clearly identifiable and separable factors, notably the length of the polyQ tract, influence the mechanism of aggregation, its associated kinetics, and the ensemble of structures formed. In this work, we examine the ability of 12 biomolecular force fields to reproduce the properties of a simple, 30-residue polyQ peptide (Q₃₀) in explicit water.

Protein Folding (Cont'd)

Chromatin Unfolding by Epigenetic Modifications Explained by Dramatic Impairment of Internucleosome Interactions: A Multiscale Computational Study

Rosana Collepardo-Guevara, Guillem Portella, Michele Vendruscolo, Daan Frenkel, Tamar Schlick, and Modesto Orozco [Universitat de Barcelona]

J. Am. Chem. Soc., **137**, 10205–10215, 2015.

Histone tails and their epigenetic modifications play crucial roles in gene expression regulation by altering the architecture of chromatin. Given the technical challenges in obtaining detailed experimental characterizations of the structure of chromatin, multiscale computations offer a promising alternative to model the effect of histone tails on chromatin folding. Here we combine multimicrosecond atomistic molecular dynamics simulations of dinucleosomes and histone tails in explicit solvent and ions, performed with three different state-of-the-art force fields and validated by experimental NMR measurements, with coarse-grained Monte Carlo simulations of 24-nucleosome arrays.

Protein folding optimization based on 3D off-lattice model via an improved artificial bee colony algorithm

Bai Li [Zhejiang University, Hangzhou], Mu Lin, Qiao Liu, Ya Li, Changjun Zhou

J. Mol.Mod., **21**, 261, 2015.

Protein folding is a fundamental topic in molecular biology. Conventional experimental techniques for protein structure identification or protein folding recognition require strict laboratory requirements and heavy operating burdens, which have largely limited their applications. Alternatively, computer-aided techniques have been developed to optimize protein structures or to predict the protein folding process. In this paper, we utilize a 3D off-lattice model to describe the original protein folding scheme as a simplified energy-optimal numerical problem, where all types of amino acid residues are binarized into hydrophobic and hydrophilic ones.

Structural Perturbations Present in the Folding Cores of Interleukin-33 and Interleukin-1 β Correlate to Differences in Their Function

V. V. Hemanth Giri Rao and Shachi Gosavi [Tata Institute of Fundamental Research, Bangalore]

J. Phys. Chem. B., **119**, 11203–11214, 2015.

The interleukin-1 cytokines belong to the β -trefoil fold family and play a key role in immune responses to infections and injury. We simulate the structure-based models of two interleukin-1 cytokines, IL-33 and IL-1 β , and find that IL-33 has a lower barrier to folding than IL-1 β . We then design the folding motif (FM) of the β -trefoil fold and identify structural deviations of IL-33 and IL-1 β from this FM. In previous work, we found that structural deviations from the FM that are large enough to lower folding free energy barriers were part of ligand binding sites. In contrast, we find that structural perturbations in IL-33 and IL-1 β which reduce the folding free energy barrier are located in the folding core and do not bind ligands.

Protein-Nucleic acid Interactions

BinDNase: a discriminatory approach for transcription factor binding prediction using DNase I hypersensitivity data

Juhani Kähärä [Aalto University School of Science] and Harri Lähdesmäki

Bioinformatics. **31**, 2852-2859, 2015.

Transcription factors (TFs) are a class of DNA-binding proteins that have a central role in regulating gene expression. To reveal mechanisms of transcriptional regulation, a number of computational tools have been proposed for predicting TF-DNA interaction sites. Here, we introduce a novel discriminative algorithm, BinDNase, for predicting TF-DNA interaction sites using DNase-seq data. BinDNase implements an efficient method for selecting and extracting informative features from DNase I signal for each TF, either at single nucleotide resolution or for larger regions. The method is applied to 57 transcription factors in cell line K562 and 31 transcription factors in cell line HepG2 using data from the ENCODE project.

Protein modeling and molecular dynamics simulation of SIWRKY4 protein cloned from drought tolerant tomato (*Solanum habrochaites*) line EC520061

Suhas G. Karkute, Muruges Easwaran, Ranjit Singh Gujjar, Shanmughavel Piramanayagam, Major Singh [Indian Institute of Vegetable Research, Varanasi]

J. Mol.Mod., **21**, 255, 2015.

WRKY genes are members of one of the largest families of plant transcription factors and play an important role in response to biotic and abiotic stresses, and overall growth and development. Understanding the interaction of WRKY proteins with other proteins/ligands in plant cells is of utmost importance to develop plants having tolerance to biotic and abiotic stresses. The SIWRKY4 gene was cloned from a drought tolerant wild species of tomato (*Solanum habrochaites*) and the secondary structure and 3D modeling of this protein were predicted using Schrödinger Suite-Prime. Predicted structures were also subjected to plot against Ramachandran's conformation, and the modeled structure was minimized using Macromodel.

Representative Amino Acid Side-Chain Interactions in Protein–DNA Complexes: A Comparison of Highly Accurate Correlated Ab Initio Quantum Mechanical Calculations and Efficient Approaches for Applications to Large Systems

Jiří Hostaš, Dávid Jakubec, Roman A. Laskowski, Ramachandran Gnanasekaran, Jan Řezáč, Jiří Vondrášek, and Pavel Hobza [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp, **11**, 4086–4092, 2015.

Representative pairs of amino acid side chains and nucleic acid bases extracted from available high-quality structures of protein–DNA complexes were analyzed using a range of computational methods. CCSD(T)/CBS interaction energies were calculated for the chosen 272 pairs. These reference interaction energies were used to test the MP2.5/CBS, MP2.X/CBS, MP2-F12, DFT-D3, PM6, and Amber force field methods. Method MP2.5 provided excellent agreement with reference data (root-mean-square error (RMSE) of 0.11 kcal/mol), which is more than 1 order of magnitude faster than the CCSD(T) method. When MP2-F12 and MP2.5 were combined, the results were within reasonable accuracy (0.20 kcal/mol), with a computational savings of almost 2 orders of magnitude.

Protein - Nucleic Acid Interactions (Cont'd)

Dynamics of the Active Sites of Dimeric Seryl tRNA Synthetase from *Methanopyrus kandleri*

Saheb Dutta and Nilashis Nandi [University of Kalyani, Kalyani]

J. Phys. Chem. B., **119**, 10832–10848, 2015.

Aminoacyl tRNA synthetases (aaRSs) carry out the first step of protein biosynthesis. Several aaRSs are multimeric, and coordination between the dynamics of active sites present in each monomer is a prerequisite for the fast and accurate aminoacylation. However, important lacunae of understanding exist concerning the conformational dynamics of multimeric aaRSs. In the present work, we carried out all-atom molecular dynamics simulation of dimeric ^{mk}SerRS from *Methanopyrus kandleri* bound with tRNA using an explicit solvent system.

Correlated Conformational Motions of the KH Domains of Far Upstream Element Binding Protein Complexed with Single-Stranded DNA Oligomers

Kaushik Chakraborty and Sanjoy Bandyopadhyay [Indian Institute of Technology, Kharagpur]

J. Phys. Chem. B., **119**, 10998–11009, 2015.

Single-stranded DNA binding (SSB) proteins bind with single-stranded DNA (ss-DNA) segments that are generated as intermediates during DNA metabolic processes. The primary function of an SSB protein is to protect the ss-DNA from being degraded so that other enzymes can effectively act on it. We have performed atomistic molecular dynamics simulations of the two DNA binding K homology (KH) domains (KH3 and KH4) of the far upstream element (FUSE) binding protein (FBP) complexed with two ss-DNA oligomers in aqueous solutions.

DNA Binding to the Silica Surface

Bobo Shi, Yun Kyung Shin, Ali A. Hassanali, and Sherwin J. Singer [The Ohio State University, Columbus]

J. Phys. Chem. B., **119**, 11030–11040, 2015.

We investigate the DNA–silica binding mechanism using molecular dynamics simulations. This system is of technological importance, and also of interest to explore how negatively charged DNA can bind to a silica surface, which is also negatively charged at pH values above its isoelectric point near pH 3. We find that the two major binding mechanisms are attractive interactions between DNA phosphate and surface silanol groups and hydrophobic bonding between DNA base and silica hydrophobic region. Umbrella sampling and the weighted histogram analysis method (WHAM) are used to calculate the free energy surface for detachment of DNA from a binding configuration to a location far from the silica surface.

Molecular Dynamics Simulations of Perylenediimide DNA Base Surrogates

Cade B. Markegard, Amir Mazaheripour, Jonah-Micah Jocson, Anthony M. Burke, Mary N. Dickson, Alon A. Gorodetsky, and Hung D. Nguyen [University of California, Irvine]

J. Phys. Chem. B., **119**, 11459–11465, 2015.

Perylene-3,4,9,10-tetracarboxylic diimides (PTCDIs) are a well-known class of organic materials. Recently, these molecules have been incorporated within DNA as base surrogates, finding ready applications as probes of DNA structure and function. However, the assembly dynamics and kinetics of PTCDI DNA base surrogates have received little attention to date. Herein, we employ constant temperature molecular dynamics simulations to gain an improved understanding of the assembly of PTCDI dimers and trimers.

Nucleic Acids

Differential Deformability of the DNA Minor Groove and Altered BI/BII Backbone Conformational Equilibrium by the Monovalent Ions Li^+ , Na^+ , K^+ , and Rb^+ via Water-Mediated Hydrogen Bonding

Alexey Savelyev and Alexander D. MacKerell, Jr. [University of Maryland, Baltimore]

J. Chem. Theor. and Comp., **11**, 4473–4485, 2015.

Recently, we reported the differential impact of the monovalent cations Li^+ , Na^+ , K^+ , and Rb^+ on DNA conformational properties. These were identified from variations in the calculated solution-state X-ray DNA spectra as a function of the ion type in solvation buffer in MD simulations using our recently developed polarizable force field based on the classical Drude oscillator. In the present study, we show that the primary microscopic mechanism for the phenomenon is the formation of water-mediated hydrogen bonds between solvated cations located inside the minor groove and simultaneously to two DNA strands, a process whose intensity and impact on DNA structure depends on both the type of ion and the DNA sequence.

DNA Elasticity from Short DNA to Nucleosomal DNA

Ashok Garai, Suman Saurabh, Yves Lansac, and Prabal K. Maiti [Indian Institute of Science, Bangalore]

J. Phys. Chem. B., **119**, 11146–11156, 2015.

Active biological processes like transcription, replication, recombination, DNA repair, and DNA packaging encounter bent DNA. Machineries associated with these processes interact with the DNA at short length (<100 base pair) scale. Thus, the study of elasticity of DNA at such length scale is very important. We use fully atomistic molecular dynamics (MD) simulations along with various theoretical methods to determine elastic properties of dsDNA of different lengths and base sequences. We also study DNA elasticity in nucleosome core particle (NCP) both in the presence and the absence of salt.

Electrophoretic Transport of Single DNA Nucleotides through Nanoslits: A Molecular Dynamics Simulation Study

Kai Xia, Brian R. Novak, Kumuditha M. Weerakoon-Ratnayake, Steven A. Soper, Dimitris E. Nikitopoulos, and Dorel Moldovan [Louisiana State University, Baton Rouge]

J. Phys. Chem. B., **119**, 11443–11458, 2015.

There is potential for flight time based DNA sequencing involving disassembly into individual nucleotides which would pass through a nanochannel with two or more detectors. We performed molecular dynamics simulations of electrophoretic motion of single DNA nucleotides through 3 nm wide hydrophobic slits with both smooth and rough walls. The electric field (E) varied from 0.0 to 0.6 V/nm. The nucleotides adsorb and desorb from walls multiple times during their transit through the slit. The nucleotide-wall interactions differed due to nucleotide hydrophobicities and wall roughness which determined duration and frequency of nucleotide adsorptions and their velocities while adsorbed.

Surfaces, Catalysts, and Materials Subjects

Modeling Aggregation of Ionic Surfactants Using a Smeared Charge Approximation in Dissipative Particle Dynamics Simulations

Runfang Mao, Ming-Tsung Lee, Aleksey Vishnyakov, and Alexander V. Neimark [the State University of New Jersey]

J. Phys. Chem. B., **119**, 11673–11683, 2015.

Using dissipative particle dynamics (DPD) simulations, we explore the specifics of micellization in the solutions of anionic and cationic surfactants and their mixtures. Anionic surfactant sodium dodecyl sulfate (SDS) and cationic surfactant cetyltrimethylammonium bromide (CTAB) are chosen as characteristic examples. Coarse-grained models of the surfactants are constructed and parameterized using a combination of atomistic molecular simulation and infinite dilution activity coefficient calibration. Electrostatic interactions of charged beads are treated using a smeared charge approximation: the surfactant heads and dissociated counterions are modeled as beads with charges distributed around the bead center in an implicit dielectric medium.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Relevance Vector Machines: Sparse Classification Methods for QSAR

Frank R. Burden and David A. Winkler [CSIRO Manufacturing Flagship]

J.Chem. Infor. and Mod. **55**, 1529–1534, 2015.

Sparse machine learning methods have provided substantial benefits to quantitative structure property modeling, as they make model interpretation simpler and generate models with improved predictivity. Sparsity is usually induced via Bayesian regularization using sparsity-inducing priors and by the use of expectation maximization algorithms with sparse priors. The focus to date has been on using sparse methods to model continuous data and to carry out sparse feature selection. We describe the relevance vector machine (RVM), a sparse version of the support vector machine (SVM) that is one of the most widely used classification machine learning methods in QSAR and QSPR.

Data Quality in the Human and Environmental Health Sciences: Using Statistical Confidence Scoring to Improve QSAR/QSPR Modeling

Fabian P. Steinmetz, Judith C. Madden, and Mark T. D. Cronin [Liverpool John Moores University]

J.Chem. Infor. and Mod. **55**, 1739–1746, 2015.

A greater number of toxicity data are becoming publicly available allowing for in silico modeling. However, questions often arise as to how to incorporate data quality and how to deal with contradicting data if more than a single datum point is available for the same compound. In this study, two well-known and studied QSAR/QSPR models for skin permeability and aquatic toxicology have been investigated in the context of statistical data quality. In particular, the potential benefits of the incorporation of the statistical Confidence Scoring (CS) approach within modeling and validation.

Quantitative Structure-Activity Relations (Cont'd)

Critically Assessing the Predictive Power of QSAR Models for Human Liver Microsomal Stability

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

J.Chem. Infor. and Mod. **55**, 1566–1575, 2015.

To lower the possibility of late-stage failures in the drug development process, an up-front assessment of absorption, distribution, metabolism, elimination, and toxicity is commonly implemented through a battery of in silico and in vitro assays. As in vitro data is accumulated, in silico quantitative structure–activity relationship (QSAR) models can be trained and used to assess compounds even before they are synthesized. Even though it is generally recognized that QSAR model performance deteriorates over time, rigorous independent studies of model performance deterioration is typically hindered by the lack of publicly available large data sets of structurally diverse compounds. Here, we investigated predictive properties of QSAR models derived from an assembly of publicly available human liver microsomal (HLM) stability data using variable nearest neighbor (v-NN) and random forest (RF) methods.

PoLi: A Virtual Screening Pipeline Based on Template Pocket and Ligand Similarity

Ambrish Roy, Bharath Srinivasan, and Jeffrey Skolnick [Georgia Institute of Technology]

J.Chem. Infor. and Mod. **55**, 1757–1770, 2015.

Often in pharmaceutical research the goal is to identify small molecules that can interact with and appropriately modify the biological behavior of a new protein target. For such proteins, ligand homology modeling, LHM, that copies ligands from homologous and perhaps evolutionarily distant template proteins, has been shown to be a powerful VS approach to identify possible binding ligands. However, if we want to target a specific pocket for which there is no homologous holo template protein structure, then LHM will not work. To address this issue, in a new pocket-based approach, PoLi, we generalize LHM by exploiting the fact that the number of distinct small molecule ligand-binding pockets in proteins is small.

Potentials and Parameters

Parametrization of macrolide antibiotics using the force field toolkit

Anna Pavlova and James C Gumbart [Georgia Institute of Technology, Atlanta]

J. Comp. Chem., **36**, 2052–2063, 2015.

Macrolides are an important class of antibiotics that target the bacterial ribosome. Computer simulations of macrolides are limited as specific force field parameters have not been previously developed for them. Here, we determine CHARMM-compatible force field parameters for erythromycin, azithromycin, and telithromycin, using the force field toolkit (ffTK) plugin in VMD. Because of their large size, novel approaches for parametrizing them had to be developed. Two methods for determining partial atomic charges, from interactions with TIP3P water and from the electrostatic potential, as well as several approaches for fitting the dihedral parameters were tested.

Potentials and Parameters (Cont'd)

Geometric description and electronic properties of the principal photosynthetic pigments of higher plants: a DFT study

Francisco Torres-Rivas, Manuel Alberto Flores-Hidalgo, Daniel Glossman-Mitnik, Diana Barraza-Jimenez [Centro de Investigación en Alimentación y Desarrollo]

J. Mol.Mod., **21**, 256, 2015.

The geometric parameters, local and global chemical reactivity parameters (such as the ionization potential, electron affinity, electronegativity, hardness, softness, chemical potential, and electrophilicity index), as well as the energy levels (HOMO/LUMO) and HOMO-LUMO energy gaps have been determined for the principal carotenoids in higher plants. DFT calculations performed using the B3LYP functional in combination with the 6-31G(d,p) (for geometric parameters) and 6-31+G(d,p) (for energy parameters) basis sets were carried out to study these structures.

On Using Atomistic Solvent Layers in Hybrid All-Atom/Coarse-Grained Molecular Dynamics Simulations

Alexander B. Kuhn, Srinivasa M. Gopal, and Lars V. Schäfer [Ruhr-University Bochum]

J. Chem. Theor. and Comp., **11**, 4460–4472, 2015.

Hybrid all-atom/coarse-grained (AA–CG) simulations in which AA solutes are embedded in a CG environment can provide a significant computational speed-up over conventional fully atomistic simulations and thus alleviate the current length and time scale limitations of molecular dynamics (MD) simulations of large biomolecular systems. On one hand, coarse graining the solvent is particularly appealing, since it typically constitutes the largest part of the simulation system and thus dominates computational cost. On the other hand, retaining atomic-level solvent layers around the solute is desirable for a realistic description of hydrogen bonds and other local solvation effects.

Large oligomeric complex structures can be computationally assembled by efficiently combining docked interfaces

Matthias Dietzen, Olga V. Kalinina [Max Planck Institute for Informatics], Katerina Taškova, Benny Kneissl, Anna-Katharina Hildebrandt, Elmar Jaenicke, Heinz Decker, Thomas Lengauer and Andreas Hildebrandt

Proteins: Stru. Fun. & Bioinf., **83**, 1887–1899, 2015.

Macromolecular oligomeric assemblies are involved in many biochemical processes of living organisms. The benefits of such assemblies in crowded cellular environments include increased reaction rates, efficient feedback regulation, cooperativity and protective functions. However, an atom-level structural determination of large assemblies is challenging due to the size of the complex and the difference in binding affinities of the involved proteins. In this study, we propose a novel combinatorial greedy algorithm for assembling large oligomeric complexes from information on the approximate position of interaction interfaces of pairs of monomers in the complex.

Molecular Dynamics

Molecular Simulations of Solved Co-crystallized X-Ray Structures Identify Action Mechanisms of PDE δ Inhibitors

Ramin Ekhteiari Salmas, Mert Mestanoglu, Mine Yurtsever, Sergei Y. Noskov, Serdar Durdagi [Bahcesehir University, Istanbul]

Biophysical Journal. **109**, 1163-1168, 2015.

PDE δ is a small protein that binds and controls the trafficking of RAS subfamily proteins. Its inhibition protects initiation of RAS signaling, and it is one of the common targets considered for oncological drug development. In this study, we used solved x-ray structures of inhibitor-bound PDE δ targets to investigate mechanisms of action of six independent all-atom MD simulations. An analysis of atomic simulations combined with the molecular mechanic-Poisson-Boltzmann solvent accessible surface area/generalized Born solvent accessible surface area calculations led to the identification of action mechanisms for a panel of novel PDE δ inhibitors.

Molecular dynamics study on protein–water interplay in the mechanogating of the bacterial mechanosensitive channel MscL

Yasuyuki Sawada, Masahiro Sokabe [Nagoya University Graduate School of Medicine]

Eur.Biophy., **44**, 531-543, 2015.

One of the goals of mechanosensitive channel (MSC) studies is to understand the underlying molecular and biophysical mechanisms of the mechano-gating process from force sensing to gate opening. We focus on the latter process and investigate the role of water in the bacterial MSC MscL, which is activated by membrane tension. We analyze the interplay between water and the gate-constituting amino acids, Leu19–Gly26, through molecular dynamics simulations.

Effects of Concentration on Like-Charge Pairing of Guanidinium Ions and on the Structure of Water: An All-Atom Molecular Dynamics Simulation Study

Dibyendu Bandyopadhyay, K. Bhanja, Sadhana Mohan, Swapan K. Ghosh, and Niharendu Choudhury [Bhabha Atomic Research Centre]

J. Phys. Chem. B., **119**, 11262–11274, 2015.

Like-charge ion-pair formation in an aqueous solution of guanidinium chloride (GdmCl) has two important facets. On one hand, it describes the role of the arginine (ARG) side chain in aggregation and dimer formation in proteins, and on the other hand, it lends support for the direct mechanism of protein denaturation by GdmCl. We employ all-atom molecular dynamics simulations to investigate the effect of GdmCl concentration on the like-charge ion-pair formation of guanidinium ions (Gdm⁺). From analyses of the radial distribution function (RDF) between the carbon atoms of two guanidinium moieties, the existence of both contact pairs and solvent-separated pairs has been observed.

QM and QM/MM

New QM/MM implementation of the DFTB3 method in the gromacs package

Tomáš Kubař [Karlsruhe Institute of Technology], Kai Welke and Gerrit Groenhof

J. Comp. Chem., **36**, 1978–1989, 2015.

The approximate density-functional tight-binding theory method DFTB3 has been implemented in the quantum mechanics/molecular mechanics (QM/MM) framework of the Gromacs molecular simulation package. We show that the efficient smooth particle–mesh Ewald implementation of Gromacs extends to the calculation of QM/MM electrostatic interactions. Further, we make use of the various free-energy functionalities provided by Gromacs and the PLUMED plugin.

Ligand Docking

Comparison of radii sets, entropy, QM methods, and sampling on MM-PBSA, MM-GBSA, and QM/MM-GBSA ligand binding energies of *F. tularensis* enoyl-ACP reductase (FabI)

Pin-Chih Su, Cheng-Chieh Tsai, Shahila Mehboob, Kirk E. Hevener and Michael E. Johnson [Idaho State University, Meridian]

J. Comp. Chem., **36**, 1859–1873, 2015.

To validate a method for predicting the binding affinities of FabI inhibitors, three implicit solvent methods, MM-PBSA, MM-GBSA, and QM/MM-GBSA were carefully compared using 16 benzimidazole inhibitors in complex with *Francisella tularensis* FabI. The data suggests that the prediction results are sensitive to radii sets, GB methods, QM Hamiltonians, sampling protocols, and simulation length, if only one simulation trajectory is used for each ligand. In this case, QM/MM-GBSA using 6 ns MD simulation trajectories together with GB^{neck2}, PM3, and the mbondi2 radii set, generate the closest agreement with experimental values ($r^2 = 0.88$).

GeauxDock: A novel approach for mixed-resolution ligand docking using a descriptor-based force field

Yun Ding, Ye Fang, Wei P. Feinstein, Jagannathan Ramanujam, David M. Koppelman, Juana Moreno, Michal Brylinski [Louisiana State University, Baton Rouge] and Mark Jarrell

J. Comp. Chem., **36**, 2013–2026, 2015.

Molecular docking is an important component of computer-aided drug discovery. In this communication, we describe GeauxDock, a new docking approach that builds on the ideas of ligand homology modeling. GeauxDock features a descriptor-based scoring function integrating evolutionary constraints with physics-based energy terms, a mixed-resolution molecular representation of protein-ligand complexes, and an efficient Monte Carlo sampling protocol. To drive docking simulations toward experimental conformations, the scoring function was carefully optimized to produce a correlation between the total pseudoenergy and the native-likeness of binding poses.

Detection of Binding Site Molecular Interaction Field Similarities

Matthieu Chartier and Rafael Najmanovich [University of Sherbrooke]

J.Chem. Infor. and Mod. **55**, 1600–1615, 2015.

Protein binding-site similarity detection methods can be used to predict protein function and understand molecular recognition, as a tool in drug design for drug repurposing and polypharmacology, and for the prediction of the molecular determinants of drug toxicity. Here, we present IsoMIF, a method able to identify binding site molecular interaction field similarities across protein families. IsoMIF utilizes six chemical probes and the detection of subgraph isomorphisms to identify geometrically and chemically equivalent sections of protein cavity pairs.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling - 60, July, 2015.

- 1-14 **Studying the binding interactions of allosteric agonists and antagonists of the CXCR4 receptor**, Jesús M. Planesas, Violeta I. Pérez-Nueno, José I. Borrell, Jordi Teixidó [Universitat Ramon Llull, Barcelona]

See Applications / Ligand Binding.

- 15-23 **Qgui: A high-throughput interface for automated setup and analysis of free energy calculations and empirical valence bond simulations in biological systems**, Geir Villy Isaksen, Tor Arne Heim Andberg, Johan Åqvist, Bjørn Olav Brandsdal [University of Tromsø]

See Applications / Free Energy Calculations.

- 24-33 **Binding specificity of polypeptide substrates in NS2B/NS3pro serine protease of dengue virus type 2: A molecular dynamics Study**, Pathumwadee Yotmanee, Thanyada Rungrotmongkol, Kanin Wichapong, Sy Bing Choi, Habibah A. Wahab, Nawee Kungwan, Supot Hannongbua [Chulalongkorn University, Bangkok]

See Applications / Medicinal Chemistry and Drug Design.

- 34-42 **Association of the anti-tuberculosis drug rifampicin with a PAMAM dendrimer**, Reinaldo G. Bellini, Ana P. Guimarães, Marco A.C. Pacheco, Douglas M. Dias, Vanessa R. Furtado, Ricardo B. de Alencastro, Bruno A.C. Horta [Universidade Federal do Rio de Janeiro]

See Applications / Medicinal Chemistry and Drug Design.

- 43-54 **Computational fishing of new DNA methyltransferase inhibitors from natural products**, Wilson Maldonado-Rojas, Jesus Olivero-Verbel [University of Cartagena], Yovani Marrero-Ponce

See Applications / Medicinal Chemistry and Drug Design.

- 55-62 **Predicting activity approach based on new atoms similarity kernel function**, Ahmed H. Abu El-Atta, M.I. Moussa, Aboul Ella Hassanien [Scientific Research Group in Egypt]

Drug design is a high cost and long term process. To reduce time and costs for drugs discoveries, new techniques are needed. Chemoinformatics field implements the informational techniques and computer science like machine learning and graph theory to discover the chemical compounds properties, such as toxicity or biological activity. These kernels methods have led to impressive performance results in many several chemoinformatics problems like biological activity prediction.

- 63-78 **Molecular descriptors calculation as a tool in the analysis of the antileishmanial activity achieved by two series of diselenide derivatives. An insight into its potential action mechanism**, María Font [Departamento de Química Orgánica y Farmacéutica], Ylenia Baquedano, Daniel Plano, Esther Moreno, Socorro Espuelas, Carmen Sanmartín, Juan Antonio Palop

See Applications / Medicinal Chemistry and Drug Design.

- 79-88 **The study of dual COX-2/5-LOX inhibitors by using electronic-topological approach based on data on the ligand–receptor interactions**, Fatma Aksakal, Natali Shvets, Anatholy Dimoglo [Gebze Technical University, Kocaeli]

See Applications / Medicinal Chemistry and Drug Design.

- 89-97 **Designing of potential inhibitors against Staphylococcus aureus sortase A: Combined analogue and structure based approach with in vitro validation**, K. Kranthi Raj, Veeramachaneni Ganesh Kumar, Chalasani Leela Madhuri, Pardhasaradhi Mathi, Ravulapati Durga Lakshmi, M. Ravi, B. Sri Ramudu, S.V. Venkata Rao, D. Ramachandran [Acharya Nagarjuna University]

See Applications / Medicinal Chemistry and Drug Design.

- 98-107 **Interaction of menthol with mixed-lipid bilayer of stratum corneum: A coarse-grained simulation study**, Guang Wan, Xingxing Dai, Qianqian Yin, Xinyuan Shi, Yanjiang Qiao [Beijing University of Chinese Medicine]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

- 108-117 **Computational prediction of octanol–water partition coefficient based on the extended solvent-contact model**, Taeho Kim, Hwangseo Park [Sejong University]

The logarithm of 1-octanol/water partition coefficient (LogP) is one of the most important molecular design parameters in drug discovery. Assuming that LogP can be calculated from the difference between the solvation free energy of a molecule in water and that in 1-octanol, we propose a method for predicting the molecular LogP values based on the extended solvent-contact model.

- 118-123 **How the cation–cation π – π stacking occurs: A theoretical investigation into ionic clusters of imidazolium**, Wei Gao, Yong Tian [Guangdong Pharmaceutical University], Xiaopeng Xuan

The cation–cation π – π stacking is uncommon but it is essential for the understanding of some supramolecular structures. We explore theoretically the nature of non-covalent interaction occurring in the stacked structure within modeled clusters of 1,3-dimethylimidazolium and halide.

- 124-131 **Structure-based virtual screening as a tool for the identification of novel inhibitors against Mycobacterium tuberculosis 3-dehydroquinase dehydratase**, Guilherme O. Petersen, Shalini Saxena, Janupally Renuka, Vijay Soni, Perumal Yogeeswari, Diogenes S. Santos, Cristiano V. Bizarro [Pontifícia Universidade Católica do Rio Grande do Sul], Dharmarajan Sriram

See Applications / Medicinal Chemistry and Drug Design.

- 132-141 **Layered SiC sheets: A promising metal-free catalyst for NO reduction**, Jing wen Feng, Yue jie Liu, Jing xiang Zhao [Harbin Normal University, Harbin]

Recently, the catalytic reduction is shown to be an effective method to remove the harmful NO. In terms of the high cost and limited supply of the traditional transition metal-based catalysts, the novel metal-free catalyst is highly desirable for NO reduction. Here, density functional theory (DFT) computations were performed to explore the potentials of layered SiC sheets as a metal-free catalyst for NO reduction.

- 142-154 **Effective virtual screening strategy focusing on the identification of novel Bruton's tyrosine kinase inhibitors**, Jianhu Xiao, Shengping Zhang, Minghao Luo, Yi Zou, Yihua Zhang, Yisheng Lai [China Pharmaceutical University]

See Applications / Medicinal Chemistry and Drug Design.

- 155-161 **Understanding the molecular mechanism and regioselectivity in the synthesis of celecoxib via a domino reaction: A DFT study**, Saeedreza Emamian [Islamic Azad University, Shahrood]

The molecular mechanism and energetic of the domino reaction involved in the synthesis of celecoxib, a well-known anti-inflammatory drug, were theoretically studied at the DFT-B3LYP/6-31G* level.

- 162-168 **Effects of imidazolium-based ionic surfactants on the size and dynamics of phosphatidylcholine bilayers with saturated and unsaturated chains**, Hwankyu Lee [Dankook University, Yongin]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

- 169-179 **Conformational properties of chiral tobacco alkaloids by DFT calculations and vibrational circular dichroism: (–)-S-anabasine**, P.G. Rodríguez Ortega, M. Montejó [University of Jaén], F. Márquez, J.J. López González

A thorough DFT and MM study of the conformational landscape, molecular and electronic structures of (–)-S-anabasine is reported aimed to reveal the mechanism controlling its conformational preference.

- 180-196 **Structural and dynamical aspects of Streptococcus gordonii FabH through molecular docking and MD simulations**, Amen Shamim, Sumra Wajid Abbasi, Syed Sikander Azam [Quaid-i-Azam University]

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 36 (25), September, 2015.

- 1859–1873 **Comparison of radii sets, entropy, QM methods, and sampling on MM-PBSA, MM-GBSA, and QM/MM-GBSA ligand binding energies of F. tularensis enoyl-ACP reductase (FabI)**, Pin-Chih Su, Cheng-Chieh Tsai, Shahila Mehboob, Kirk E. Hevener and Michael E. Johnson [Idaho State University, Meridian]

See Methodology / Ligand Docking.

- 1874–1884 **Transferability and additivity of dihedral parameters in polarizable and nonpolarizable empirical force fields**, Marie Zgarbová, Andreana M. Rosnik, F. Javier Luque, Carles Curutchet [Universitat de Barcelona, Barcelona] and Petr Jurečka

Recent advances in polarizable force fields have revealed that major reparameterization is necessary when the polarization energy is treated explicitly. This study is focused on the torsional parameters, which are crucial for the accurate description of conformational equilibria in biomolecules.

- 1885–1892 **Understanding the basis of I50V-induced affinity decrease in HIV-1 protease via molecular dynamics simulations using polarized force field**, Rui Duan, Raudah Lazim and Dawei Zhang [Nanyang Technological University]

See Applications / Medicinal Chemistry and Drug Design.

- 1893–1901 **A new QM/MM method oriented to the study of ionic liquids**, M. Luz Sánchez, José C. Corchado, M. Elena Martín, Ignacio Fdez. Galván, Rute Barata-Morgado and Manuel A. Aguilar [University of Extremadura]

The interest on room temperature ionic liquids has grown in the last decades because of their use as all-purpose solvent and their low environmental impact. In the present work, a new theoretical procedure is developed to study pure ionic liquids within the framework of the quantum mechanics/molecular mechanics method.

- 1902–1906 **An enhanced Monte Carlo outlier detection method**, Liangxiao Zhang, Peiwu Li [Chinese Academy of Agricultural Sciences], Jin Mao, Fei Ma, Xiaoxia Ding and Qi Zhang

Outlier detection is crucial in building a highly predictive model. In this study, we proposed an enhanced Monte Carlo outlier detection method by establishing cross-prediction models based on determinate normal samples and analyzing the distribution of prediction errors individually for dubious samples.

- 1907–1918 **A topological assessment of the electronic structure of mesoionic compounds**, Italo Curvelo Anjos and Gerd Bruno Rocha [Universidade Federal da Paraíba, João Pessoa]

Mesoionic compounds belonging to the 1,3-oxazol-5-one, 1,3-diazole-4-thione and 1,3-thiazole-5-thione rings have been evaluated by a combination of Density Functional Theory, Quantum Theory of Atoms in Molecules, Electron Localization Function, Natural Bond Orbitals and Geodesic Electrostatic Potential Charge calculations.

- 1919–1927 **Van der Waals Effects on semiconductor clusters**, Haisheng Li, Weiguang Chen, Xiaoyu Han, Liben Li, Qiang Sun, Zhengxiao Guo and Yu Jia [Zhengzhou University, Zhengzhou]

Van der Waals (vdW) interactions play an important role on semiconductors in nanoscale. Here, we utilized first-principles calculations based on density functional theory to demonstrate the growth mode transition from prolate to multiunit configurations for Ge_n ($n = 10\text{--}50$) clusters.

Journal of Computational Chemistry, 36 (26), October, 2015.

- 1929–1939 **Probing the range of applicability of structure- and energy-adjusted QM/MM link bonds**, Manuel Hitzenberger and Thomas S. Hofer [University of Innsbruck]

The hydrogen-capping method is one of the most popular and widely used coupling-schemes for quantum mechanics/molecular mechanics (QM/MM)-molecular dynamics simulations of macromolecular systems. To further increase the accuracy, instead of global parameters for all amino acids, different parameter sets for each type of amino acid are derived.

- 1940–1946 **Electron density analysis of large (molecular and periodic) systems: A parallel implementation**, Silvia Casassa [Università di Torino and NIS], Alessandro Erba, Jacopo Baima and Roberto Orlando

A parallel implementation is presented of a series of algorithms for the evaluation of several one-electron properties of large molecular and periodic (of any dimensionality) systems. The electron charge and momentum densities of the system, the electrostatic potential, X-ray structure factors, directional Compton profiles can be effectively evaluated at low computational cost along with a full topological analysis of the electron charge density (ECD) of the system according to Bader's quantum theory of atoms in molecules.

- 1947–1953 **Computational assessment of electron density in metallo-organic nickel pincer complexes for formation of P—C bonds**, Joshua J. Eller and Karen Downey [State University of New York College at Cortland]

Hydrophosphination is an atomically efficient method for introducing new carbon-phosphorous bonds in organic synthesis. New late-transition metal catalytic complexes are proposed to facilitate this process. These nickel-based complexes are analyzed using semiempirical (SE), Hartree–Fock (H–F), and density functional theory (DFT) models.

- 1954–1972 **Relativistic state-specific multireference perturbation theory incorporating improved virtual orbitals: Application to the ground state single-bond dissociation**, Anirban Ghosh, Rajat K. Chaudhuri, Sudip Chattopadhyay [Indian Institute of Engineering Science and Technology] and Uttam Sinha Mahapatra

Using four-component (4c) relativistic spinors, we present a computationally economical relativistic ab initio method for molecular systems employing our recently proposed second-order state-specific multireference perturbation theory (SSMRPT) incorporating the improved virtual orbital-complete active space configuration interaction (IVO-CASCI) reference wavefunction.

- 1973–1977 **AquaBridge: A novel method for systematic search of structural water molecules within the protein active sites**, Arina Afanasyeva [St. Petersburg State Polytechnical University], Sergey Izmailov, Michel Grigoriev and Michael Petukhov

See Applications / Protein Dynamics.

- 1978–1989 **New QM/MM implementation of the DFTB3 method in the gromacs package**, Tomáš Kubař [Karlsruhe Institute of Technology], Kai Welke and Gerrit Groenhof

See Methodology / QM and QM/MM.

1990–2008 **Best bang for your buck: GPU nodes for GROMACS biomolecular simulations**, Carsten Kutzner [Max Planck Institute for Biophysical Chemistry, Göttingen], Szilárd Páll, Martin Fechner, Ansgar Esztermann, Bert L. de Groot and Helmut Grubmüller

See Applications / Bioinformatics.

Journal of Computational Chemistry, 36 (27), October, 2015.

2013–2026 **GeauxDock: A novel approach for mixed-resolution ligand docking using a descriptor-based force field**, Yun Ding, Ye Fang, Wei P. Feinstein, Jagannathan Ramanujam, David M. Koppelman, Juana Moreno, Michal Brylinski [Louisiana State University, Baton Rouge] and Mark Jarrell

See Methodology / Ligand Docking.

2027–2036 **Effect of methylation on relative energies of tautomers and on the intramolecular proton transfer barriers of protonated nitrosamine: A MR-CISD study**, Railton Barbosa de Andrade, Ezequiel Fragoso Vieira Leitão, Miguel Angelo Fonseca de Souza, Elizete Ventura and Silmar Andrade do Monte [Universidade Federal da Paraíba]

MR-CISD, MR-CISD+Q, and MR-AQCC calculations have been performed on the minima and transition states (corresponding to intramolecular proton transfer between the protonation sites) of the ground state of protonated nitrosamine and N,N-dimethylnitrosamine.

2037–2043 **Modeling exact exchange potential in spherically confined atoms**, Sergei F. Vyboishchikov [Universitat de Girona, Girona]

In this work, local exchange potentials corresponding to the Hartree–Fock (HF) electron density have been obtained using the Zhao–Morrison–Parr method for a number of closed-shell confined atoms and ions.

2044–2051 **Enhanced stability of the model mini-protein in amino acid ionic liquids and their aqueous solutions**, Guillaume Chevrot, Eudes Eterno Fileti [Universidade Federal de São Paulo] and Vitaly V. Chaban

See Applications / Protein Dynamics.

2052–2063 **Parametrization of macrolide antibiotics using the force field toolkit**, Anna Pavlova and James C Gumbart [Georgia Institute of Technology, Atlanta]

See Methodology / Potentials and Parameters.

2064–2074 **Application of a BOSS—Gaussian interface for QM/MM simulations of Henry and methyl transfer reactions**, Jonah Z. Vilseck, Jakub Kostal, Julian Tirado-Rives and William L. Jorgensen [Yale University, New Haven]

Hybrid quantum mechanics and molecular mechanics (QM/MM) computer simulations have become an indispensable tool for studying chemical and biological phenomena for systems too large to treat with QM alone. For several decades, semiempirical QM methods have been used in QM/MM simulations.

- 2075–2087 **SCC-DFTB parameters for simulating hybrid gold-thiolates compounds**, Arnaud Fihey, Christian Hettich, Jérémy Touzeau, François Maurel, Aurélie Perrier, Christof Köhler, Bálint Aradi [Universität Bremen, Bremen] and Thomas Frauenheim

We present a parametrization of a self-consistent charge density functional-based tight-binding scheme (SCC-DFTB) to describe gold-organic hybrid systems by adding new Au-X (X = Au, H, C, S, N, O) parameters to a previous set designed for organic molecules.

Journal of Molecular Modeling, 21 (10), October, 2015.

- 268 **Empirical force field for cisplatin based on quantum dynamics data: case study of new parameterization scheme for coordination compounds**, S. Yesylevskyy, Bruno Cardey, S. Kraszewski, Sarah Foley, Mironel Enescu, Antônio M. da Silva Jr., Hélio F. Dos Santos, Christophe Ramseyer [Université de Franche-Comté]

Parameterization of molecular complexes containing a metallic compound, such as cisplatin, is challenging due to the unconventional coordination nature of the bonds which involve platinum atoms. In this work, we develop a new methodology of parameterization for such compounds based on quantum dynamics (QD) calculations.

- 267 **Thermodynamic analysis of fuels in gas phase: ethanol, gasoline and ethanol — gasoline predicted by DFT method**, A. F. G. Neto [Federal University of Pará], F. S. Lopes, E. V. Carvalho, M. N. Huda, A. M. J. C. Neto, N. T. Machado

This paper presents a theoretical study using density functional theory to calculate thermodynamics properties of major molecules compounds at gas phase of fuels like gasoline, ethanol, and gasoline–ethanol mixture in thermal equilibrium on temperature range up to 1500 K.

- 266 **On the correction of calculated vibrational frequencies for the effects of the counterions — α,ω -diamine dihydrochlorides**, S. M. Fiuza, T. M. Silva, M. P. M. Marques, L. A. E. Batista de Carvalho, A. M. Amado [University of Coimbra]

The present work provides sets of correction factors to adjust the calculated vibrational frequencies of a series of α,ω -diamines hydrochloride salts to account for the intermolecular interactions with the counterion. The study was performed using different theory levels for predicting the vibrational data of isolated dicationic α,ω -diamines and their hydrochloride forms, with and without the explicit account of the interactions with the chloride counterions.

- 265 **Trapping N₅ rings and N₃ chains on the outer surface of fullerene C₆₀: a theoretical study**, Yanhong Liang, Xiaozhen Gao, Nan Li [Beijing Institute of Technology, Beijing], Xiuhui Zhang

The capture of N₃-chains and N₅-rings on the outer surface of C₆₀ was studied using density functional calculations. For the neutral N₅-ring, it was found that a N₅-ring trapped by a C₆₀ cage becomes more stable than an isolated N₅-ring radical, and a C₆₀–N₅ compound with a C–N bond at an exohedral position of C₆₀ is more stable than an isomer with the N₅-ring encapsulated in C₆₀.

- 264 **Computational studies on the regioselectivity of metal-catalyzed synthesis of 1,2,3 triazoles via click reaction: a review**, Tayebbeh Hosseinejad, Bahareh Fattahi, Majid M. Heravi [Alzahra University, Vanak]

Recently, the experimental and computational chemists have been attracted widely to the click synthesis of 1,2,3 triazoles and their derivatives, mainly due to the fact that they are interesting from structural and mechanistic points of view. In this review, we try to highlight the recently reported computational assessments on the origins and prediction of regioselectivity in the catalyzed click synthesis of triazoles from the mechanistic and thermodynamical points of view.

- 263 **Molecular modeling of amorphous, non-woven polymer networks**, Constantin A. Krausse, Theodor Milek, Dirk Zahn [Friedrich-Alexander Universität Erlangen-Nürnberg]

We outline a simple and efficient approach to generating molecular models of amorphous polymer networks. Similar to established techniques of preparing woven polymer networks from quenching high-temperature molecular simulation runs, we use a molecular dynamics simulations of a generic melt as starting points.

- 262 **Impact sensitivity and the maximum heat of detonation**, Peter Politzer [University of New Orleans, New Orleans], Jane S. Murray

We demonstrate that a large heat of detonation is undesirable from the standpoint of the impact sensitivity of an explosive and also unnecessary from the standpoints of its detonation velocity and detonation pressure. High values of the latter properties can be achieved even with a moderate heat of detonation, and this in turn enhances the likelihood of relatively low sensitivity.

- 261 **Protein folding optimization based on 3D off-lattice model via an improved artificial bee colony algorithm**, Bai Li [Zhejiang University, Hangzhou], Mu Lin, Qiao Liu, Ya Li, Changjun Zhou

See Applications / Protein Folding.

- 260 **DFT studies on the palladium-catalyzed dearomatization reaction between naphthalene allyl chloride and allyltributylstannane**, Wei Cao, Dongxu Tian [Dalian University of Technology, Dalian], Dongxue Han

The Pd-catalyzed dearomatization of naphthalene allyl chloride with allyltributylstannane has been investigated using density functional theory (DFT) calculations at the B3LYP level.

- 259 **“Dancing inside the ball”: the structures and nonlinear optical properties of three $\text{Sc}_2\text{S}@C_{3v}(8)-C_{82}$ isomers**, Feng-Wei Gao, Ying Gao, Li-Jie Wang, Hong-Liang Xu, Shi-Ling Sun [Northeast Normal University, Changchun], Zhong-Min Su

Recently, the crystal structures and electrochemical properties of the isomers (Sc_2S “trapped” in C_{82}) have been reported, in which the Sc_2S is located inside the different positions of the C_{82} cage. In the present work, three isomers of endohedral metallofullerenes $\text{Sc}_2\text{S}@C_{3v}(8)-C_{82}$ (**A**, **B**, and **C**) have been designed to explore the effect of the position of Sc_2S on their interaction energies and nonlinear optical properties.

- 258 **Charge transfer and first hyperpolarizability: cage-like radicals $C_{59}X$ and lithium encapsulated $\text{Li}@C_{59}X$ ($X=\text{B}$, N)**, Feng-Wei Gao, Rong-Lin Zhong, Shi-Ling Sun, Hong-Liang Xu, Liang Zhao, Zhong-Min Su [Northeast Normal University, Changchun]

Very recently, two new cage-like radicals ($C_{59}B$ and $C_{59}N$) formed by a boron or nitrogen atom substituting one carbon atom of C_{60} were synthesized and characterized. In order to explore the structure–property relationships of combination the cage-like radical and alkali metal, the endohedral $Li@C_{59}B$ and $Li@C_{59}N$ are designed by lithium (Li) atom encapsulated into the cage-like radicals $C_{59}B$ and $C_{59}N$.

- 257 **Synergistic and diminutive effects between halogen bond and lithium bond in complexes involving aromatic compounds**, Mingxiu Liu, Mengyang Cai, Qingzhong Li [Yantai University, Yantai], Wenzuo Li, Jianbo Cheng

Quantum chemical calculations have been performed to study the interplay between halogen bond and lithium bond in the ternary systems $FX-C_6H_5CN-LiF$, $FLi-C_6H_5CN-XF$, and $FLi-C_6H_5X-NH_3$ ($X = Cl, Br, \text{ and } I$) involving aromatic compounds.

- 256 **Geometric description and electronic properties of the principal photosynthetic pigments of higher plants: a DFT study**, Francisco Torres-Rivas, Manuel Alberto Flores-Hidalgo, Daniel Glossman-Mitnik, Diana Barraza-Jimenez [Centro de Investigación en Alimentación y Desarrollo]

See Methodology / Potentials and Parameters.

- 255 **Protein modeling and molecular dynamics simulation of SIWRKY4 protein cloned from drought tolerant tomato (*Solanum habrochaites*) line EC520061**, Suhas G. Karkute, Muruges Easwaran, Ranjit Singh Gujjar, Shanmughavel Piramanayagam, Major Singh [Indian Institute of Vegetable Research, Varanasi]

See Applications / Protein-Nucleic acids.

- 254 **Second hyperpolarizability of delta shaped disubstituted acetylene complexes of beryllium, magnesium, and calcium**, Kaushik Hatua, Prasanta K. Nandi [Indian Institute of Engineering Science and Technology, Shibpur]

Present theoretical study involves the delta shape complexes of beryllium, magnesium, and calcium where the metal atom interacts perpendicularly with disubstituted acetylene. Most of the complexes are found to be fairly stable.

- 253 **Simultaneous interactions of pyrimidine ring with BeF_2 and BF_3 in $BeF_2 \cdots X-Pyr \cdots BF_3$ complexes: non-cooperativity**, Saber Ghafari, Alireza Gholipour [Islamic Azad University, Khoramabad]

We investigated the mutual interplay between beryllium and boron bonds in the $BeF_2 \cdots X-Pyr \cdots BF_3$ complexes ($X = CN, F, Cl, Br, H, CH_3, OH$ and NH_2 , where Pyr and $\cdots$ denote pyrimidine ring and beryllium and boron bonds, respectively) at the M06-2X/aug-cc-pVDZ level of theory.

- 252 **A user-friendly web portal for analyzing conformational changes in structures of *Mycobacterium tuberculosis***, Sameer Hassan, Manonanthini Thangam, Praveen Vasudevan, G. Ramesh Kumar, Rahul Unni, P. K. Gayathri Devi, Luke Elizabeth Hanna [National Institute for Research in Tuberculosis, Chetpet]

See Applications / Protein Conformational Analysis.

- 251 **Computational approaches to study the effects of small genomic variations**, Kamil Khafizov [Moscow Institute of Physics and Technology], Maxim V. Ivanov, Olga V. Glazova, Sergei P. Kovalenko

Advances in DNA sequencing technologies have led to an avalanche-like increase in the number of gene sequences deposited in public databases over the last decade as well as the detection of an enormous number of previously unseen nucleotide variants therein. In this review, we summarize the major computational approaches and tools that are aimed at the prediction of the functional effect of mutations, and describe the state-of-the-art databases that can be used to obtain information about mutation significance.

- 250 **Comparative molecular field analysis and molecular dynamics studies of α/β hydrolase domain containing 6 (ABHD6) inhibitors**, Agnieszka A. Kaczor [Medical University of Lublin], Katarzyna M. Targowska-Duda, Jayendra Z. Patel, Teija Parkkari, Yahaya Adams, Tapio J. Nevalainen, Antti Poso

See Applications / Enzyme Catalysis.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

A. F. G. Neto
abelfgn@yahoo.com.br
Laboratory of Preparation and Computation of Nanomaterials (LPCN),
c. C. P. 479,
66075-110, Belém, PA, Brazil

A. M. Amado
amado.am@gmail.com
I&D Unit "Química-Física Molecular",
Department of Chemistry,
Faculty of Science and Technology,
University of Coimbra, P-3004-535,
Coimbra, Portugal

Aboul Ella Hassanien
abo@egyptscience.net
Scientific Research Group in Egypt (SRGE)1,
Egypt

Adolfo B. Poma
poma@ifpan.edu.pl
Institute of Physics,
Polish Academy of Sciences,
Aleja Lotników 32/46,
02-668 Warsaw, Poland

Agnieszka A. Kaczor
agnieszka.kaczor@umlub.pl
Department of Synthesis and Chemical Technology of Pharmaceutical Substances with Molecular Modeling Laboratory,
Faculty of Pharmacy with Division of Medical Analytics,
Medical University of Lublin,
4a Chodźki St., 20059, Lublin, Poland

Alan Grossfield
alan_grossfield@urmc.rochester.edu
Department of Biochemistry and Biophysics,
University of Rochester Medical Center,
Rochester, New York

Alessandro Marrone
amarrone@unich.it
Department of Pharmacy,
Università "G D'Annunzio" Di Chieti-Pescara,
Italy

Alexander D. MacKerell, Jr.
alex@outerbanks.umaryland.edu
Department of Pharmaceutical Sciences,
School of Pharmacy, University of Maryland,
Baltimore, Maryland 21201,
United States

Alexander V. Neimark
aneimark@rutgers.edu
Department of Chemical Engineering, Rutgers,
the State University of New Jersey,
98 Brett Road, Piscataway,
New Jersey 08854, United States

Alexey V. Onufriev
alexey@cs.vt.edu
Department of Biomedical Engineering and Mechanics,
Department of Computer Science, and
Departments of Computer Science and Physics,
Virginia Tech, Blacksburg,
Virginia 24060, United States

Alireza Gholipour
Alir.gholipour@gmail.com
Young Researchers and Elite Club,
Khoramabad Branch,
Islamic Azad University,
Khoramabad, Iran

Anatholy Dimoglo
dimoglo@gtu.edu.tr
Department of Environmental Engineering,
Gebze Technical University,
Kocaeli, Turkey

Anders Wallqvist
Sven.A.Wallqvist.civ@mail.mil
DoD Biotechnology High Performance Computing Software Applications Institute,
Telemedicine and Advanced Technology Research Center,
U.S. Army Medical Research and Materiel Command,
MCMR-TT, 504 Scott Street, Fort Detrick,
Maryland 21702-5012, United States

Anirban Bhunia
abhunia@umich.edu
Department of Biophysics,
Bose Institute, P-1/12,
CIT Scheme VII M,
Kolkata 700054, India

Arina Afanasyeva
arina.afan@gmail.com
Institute of Nanobiotechnologies,
St. Petersburg State Polytechnical University,
Saint-Petersburg, Russia

Bai Li, Mu Lin
libaioutstanding@163.com
College of Control Science and Engineering,
Zhejiang University, Hangzhou,
310027, China

Beena Rai
beena.rai@tcs.com
Tata Research Development and Design Centre,
Tata Consultancy Services, 54B,
Hadapsar Industrial Estate,
Pune - 411013, India

Bjørn Olav Brandsdal
bjorn-olav.brandsdal@uit.no
The Centre for Theoretical and Computational Chemistry,
Department of Chemistry,
University of Tromsø,
N9037 Tromsø, Norway

Bruno A.C. Horta
bruno@iq.ufrj.br
Instituto de Química,
Universidade Federal do Rio de Janeiro,
Rio de Janeiro, Brazil

Byung-Chang Suh
bcsuh@dgist.ac.kr
Department of Brain and Cognitive Sciences,
Daegu Gyeongbuk Institute of Science and Technology,
Daegu, South Korea

Bálint Aradi
aradi@uni-bremen.de
Bremen Center for Computational Materials Science (BCCMS),
Universität Bremen, Bremen,
Germany

Carles Curutchet
carles.curutchet@ub.edu
Departament de Fisicoquímica,
Facultat de Farmàcia,
Universitat de Barcelona,
Barcelona,
Spain

Carsten Kutzner
ckutzne@gwdg.de
Theoretical and Computational Biophysics Department,
Max Planck Institute for Biophysical Chemistry,
Göttingen, Germany

Charusita Chakravarty
charus@chemistry.iitd.ernet.in
Department of Chemistry,
Indian Institute of Technology-Delhi,
New Delhi 110016, India

Christophe Ramseyer
christophe.ramseyer@univ-fcomte.fr
Laboratoire Chrono Environnement UMR CNRS 6249,
Université de Franche-Comté,
16 route de Gray, 25030, Besançon Cedex, France

Cristiano V. Bizarro
cristiano.bizarro@puccs.br
Centro de Pesquisas em Biologia Molecular e Funcional (CPBMF),
Instituto Nacional de Ciência e Tuberculose (INCT-TB),
Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS),
Av. Ipiranga 6681, 90619-900 Porto Alegre, Brazil

D. Ramachandran
dittakavirc@gmail.com
Department of Chemistry,
Acharya Nagarjuna University,
Nagarjuna Nagar, Guntur 522 510, India

David A. Winkler
dave.winkler@csiro.au
CSIRO Manufacturing Flagship,
Clayton South, Victoria 3169, Australia

David D. Busath
david_busath@byu.edu
Department of Physiology and Developmental Biology,
Brigham Young University, Provo,
Utah 84602, United States

Dawei Zhang
zhangdw@ntu.edu.sg
Division of Chemistry and
Biological Chemistry,
School of Physical and
Mathematical Sciences,
Nanyang Technological University,
Singapore, Singapore

Diana Barraza-Jimenez
dianabarraz@ujed.mx
Centro de Investigación en
Alimentación y Desarrollo,
A.C. Unidad Delicias. Av. 4ª Sur
3820,
Fracc. Vencedores del Desierto.
Cd.,
Delicias Chih, México, 33089

Dirk Zahn
Dirk.Zahn@chemie.uni-
erlangen.de
Computer Chemie Centrum,
Friedrich-Alexander Universität
Erlangen-Nürnberg,
Nägelsbachstraße 25, 91052,
Erlangen, Germany

Dmitri K. Klimov
dklimov@gmu.edu
School of Systems Biology,
George Mason University,
Manassas,
Virginia 20110, United States

Do-Nyun Kim
dnkim@snu.ac.kr
Department of Mechanical and
Aerospace Engineering,
Seoul National University,
Gwanak-ro 1,
Gwanak-gu, Seoul 08862,
Republic of Korea

Dong-Qing Wei
dqwei@sjtu.edu.cn
State Key Laboratory of Microbial
Metabolism and
School of Life Sciences and
Biotechnology,
Shanghai Jiao Tong University,
800 Dongchuan Road,
Shanghai 200240, China

Dongxu Tian
tiandx@dlut.edu.cn
State Key Laboratory of Fine
Chemicals,
Dalian University of Technology,
Dalian, 116024, China

Dorel Moldovan
dmoldo1@lsu.edu
Department of Mechanical and
Industrial Engineering,
Louisiana State University, Baton
Rouge,
Louisiana 70803, United States

Douglas E. V. Pires
dpires@dcc.ufmg.br
Department of Computer Science,
Universidade Federal de Minas
Gerais, Brazil

Dužanka Janežič
dusanka.janezic@upr.si
Faculty of Mathematics,
Natural Sciences and Information
Technologies,
University of Primorska,
Glagoljaška 8,
SI-6000, Koper, Slovenia

Eudes Eterno Fileti
fileti@gmail.com
Instituto de Ciência e Tecnologia,
Universidade Federal de São Paulo,
São José dos Campos,
São Paulo, Brazil

Gennady M. Verkhivker
verkhivk@chapman.edu
Graduate Program in
Computational and Data Sciences,
Department of Computational
Sciences,
Schmid College of Science and
Technology,
Chapman University, One
University Drive,
Orange, California 92866, United
States

Gerd Bruno Rocha
gbr@quimica.ufpb.br
Departamento de Química, CCEN,
Universidade Federal da Paraíba,
João Pessoa,
Paraíba, Brazil

Gregory L. Warren
greg@eyesopen.com
OpenEye Scientific Software,
9 Bisbee Court, Santa Fe,
New Mexico 87508, United States

Günther H. Peters
ph@kemi.dtu.dk
Department of Chemistry,
Technical University of Denmark,
Kongens Lyngby, Denmark

Hung D. Nguyen
hdu@uci.edu
Department of Chemical
Engineering and Materials Science,
University of California, Irvine,
Irvine, California 92697, United
States

Hwangseo Park
hspark@sejong.ac.kr
Department of Bioscience and
Biotechnology,
Sejong University, 209
Neungdong-ro,

Gwangjin-gu, Seoul 143-747,
Republic of Korea

Hwanky Lee
leeh@dankook.ac.kr
Department of Chemical
Engineering,
Dankook University,
Yongin 448-701, South Korea

Ioan Kosztin
kosztini@missouri.edu
Department of Physics and
Astronomy,
University of Missouri, Columbia,
Missouri 65211

James C Gumbart
gumbart@physics.gatech.edu
School of Physics and School of
Chemistry,
Georgia Institute of Technology,
Atlanta, Georgia

Jeffrey Skolnick
skolnick@gatech.edu
Center for the Study of Systems
Biology,
Georgia Institute of Technology,
250 14th Street NW, Atlanta,
Georgia 30318, United States

Jesus Olivero-Verbel
joliverov@unicartagena.edu.co
Environmental and Computational
Chemistry Group,
School of Pharmaceutical Sciences,
Zaragocilla Campus, University of
Cartagena,
130015 Cartagena, Colombia

Jie Zheng
zhengji@uakron.edu
Department of Chemical and
Biomolecular Engineering,
The University of Akron, Akron,
Ohio 44325, United States

Jing xiang Zhao
xjz_hmily@163.com
College of Chemistry and
Chemical Engineering,
Harbin Normal University, Harbin,
150025, People's Republic of
China

Jochen S. Hub
jhub@gwdg.de
Georg-August-University
Göttingen,
Institute for Microbiology and
Genetics,
37077 Göttingen, Germany

Jordi Martí
jordi.marti@upc.edu
Department of Physics and Nuclear
Engineering,

Technical University of Catalonia-
Barcelona Tech,
B4-B5 Northern Campus, Jordi
Girona 1-3,
08034 Barcelona, Catalonia, Spain

Jordi Teixidó
jordi.teixido@iqs.edu
Grup d'Enginyeria Molecular,
Institut Químic de Sarrià (IQS),
Universitat Ramon Llull,
Barcelona, Spain

Juan J. de Pablo
depablo@uchicago.edu
Institute for Molecular
Engineering,
University of Chicago, Chicago,
Illinois

Juhani Kähärä
juhani.kahara@aalto.fi
Department of Information and
Computer Science,
Aalto University School of
Science,
FI-00076 Aalto, Finland

Kamil Khafizov
kkhafizov@gmail.com
Moscow Institute of Physics and
Technology,
Dolgoprudny, Moscow Region,
Russian Federation

Karen Downey
Karen.Downey@cortland.edu
Department of Chemistry,
State University of New York
College at Cortland,
Cortland, New York

Lars V. Schäfer
lars.schaefer@ruhr-uni-bochum.de
Lehrstuhl für Theoretische Chemie,
Ruhr-University Bochum,
D-44780 Bochum, Germany

Liao Y. Chen
Liao.Chen@utsa.edu
Department of Physics,
University of Texas at San
Antonio,
One UTSA Circle, San Antonio,
Texas 78249, United States

Luke Elizabeth Hanna
hannatrc@yahoo.com
Department of Biomedical
Informatics,
National Institute for Research in
Tuberculosis,
Chetpet, Chennai, 600 031, India

M. Montejó
mmontejó@ujaen.es
Physical and Analytical Chemistry
Department,
Experimental Science Faculty,

University of Jaén,
Campus "Las Lagunillas",
Ed. B3, Jaén E-23071, Spain

M. Paul Gleeson
paul.gleeson@ku.ac.th
Department of Chemistry,
Faculty of Science, Kasetsart
University,
Chatuchak, Bangkok 10903,
Thailand

Majid M. Heravi
mmh1331@yahoo.com
Department of Chemistry,
Alzahra University, Vanak,
Tehran, Iran

Major Singh
singhvns@gmail.com
Division of Crop Improvement,
Indian Institute of Vegetable
Research,
Varanasi, 221305, UP, India

Manuel A. Aguilar
maguilar@unex.es
Área de Química Física,
University of Extremadura,
planta Badajoz, Spain

Marco Cecchini
mcecchini@unistra.fr
Laboratoire d'Ingénierie des
Fonctions Moléculaires Institut de
Science et d'Ingénierie
Supramoléculaires,
Université de Strasbourg,
8 allée Gaspard Monge,
F-67083 Strasbourg Cedex, France

Mark T. D. Cronin
M.T.Cronin@ljamu.ac.uk
School of Pharmacy and
Chemistry,
Liverpool John Moores University,
Byrom Street, Liverpool, L3 3AF,
England

María Font
mfont@unav.es
Sección de Modelización
Molecular,
Departamento de Química
Orgánica y Farmacéutica,
Spain

María Herrero-Zazo
mhzazo@pa.uc3m.es
Department of Computer Science,
Universidad Carlos III de Madrid,
Leganés 28911, Madrid, Spain

Masahiro Sokabe
msokabe@med.nagoya-u.ac.jp
Mechanobiology Laboratory,
Nagoya University Graduate
School of Medicine,
65 Tsurumai-cho, Showa-ku,

Nagoya, 466-8550, Japan

Matthias Rarey
rarey@zbh.uni-hamburg.de
Center for Bioinformatics,
University of Hamburg,
Bundesstrasse 43,
20146 Hamburg, Germany

Matthias Rarey
rarey@zbh.uni-hamburg.de
University of Hamburg, Center for
Bioinformatics (ZBH),
Bundesstrasse 43, 20146 Hamburg,
Germany

Michael E. Johnson
mjohnson@uic.edu
Department of Biomedical and
Pharmaceutical Sciences,
College of Pharmacy,
Idaho State University, Meridian,
Idaho

Michal Brylinski
michal@brylinski.org
Department of Physics and
Astronomy,
Louisiana State University, Baton
Rouge,
Louisiana

Michelle L. Lamb
michelle.lamb@astrazeneca.com
Oncology and Infection Innovative
Medicines Units,
AstraZeneca R&D Boston, 35
Gatehouse Drive,
Waltham, Massachusetts 02451,
United States

Modesto Orozco
modesto.oroazco@irbbarcelona.org
Departament de Bioquímica i
Biologia Molecular,
Facultat de Biologia, Universitat de
Barcelona,
Avgda Diagonal 643, 08028,
Barcelona, Spain

N. Arul Murugan
murugan@theochem.kth.se
Division of Theoretical Chemistry
and Biology,
School of Biotechnology,
KTH Royal Institute of
Technology,
SE-10691 Stockholm, Sweden

Nan Li, Xiuhui Zhang
leen04@163.com
State Key Laboratory of Explosion
Science and Technology,
School of Mechatronical
Engineering, School of Chemistry,
Beijing Institute of Technology,
Beijing,
100081, People's Republic of
China

Niharendu Choudhury
niharc2007@gmail.com
Heavy Water Division,
Bhabha Atomic Research Centre,
Mumbai 400 085, India

Nikolay V. Dokholyan
dokh@unc.edu
Department of Biochemistry &
Biophysics,
University of North Carolina,
Chapel Hill, NC, 27599, USA

Nilashis Nandi
nilashisnandi@yahoo.com
Department of Chemistry,
University of Kalyani, Kalyani,
Nadia,
West Bengal 741235, India

Nouri Neamati
neamati@umich.edu
Department of Medicinal
Chemistry,
College of Pharmacy, and
Translational Oncology Program,
University of Michigan, North
Campus Research Complex,
2800 Plymouth Road, Ann Arbor,
Michigan 48109, United States

Olga V. Kalinina
kalinina@mpi-inf.mpg.de
Max Planck Institute for
Informatics,
Campus E1 4,
66123 Saarbrücken, Germany

Paolo Carloni
p.carloni@fz-juelich.de
Computational Biophysics,
German Research School for
Simulation Sciences,
52425 Jülich, Germany

Parbati Biswas
pbiswas@chemistry.du.ac.in
Department of Chemistry,
University of Delhi,
Delhi - 110007, India

Pau Gorostiza
pau@icrea.cat
Networking Biomedical Research
Center on Bioengineering,
Biomaterials and Nanomedicine
(CIBER-BBN),
Madrid 28029, Spain

Pavel Hobza
pavel.hobza@uochb.cas.cz
Institute of Organic Chemistry and
Biochemistry,
Academy of Sciences of the Czech
Republic,
166 10 Prague, Czech Republic

Peiwu Li

peiwuli@oilcrops.cn
Oil Crops Research Institute,
Chinese Academy of Agricultural
Sciences,
Wuhan, China

Peter Politzer, Jane S. Murray
ppolitze@uno.edu
Department of Chemistry,
University of New Orleans,
New Orleans, LA, 70148, USA

Pitchairaj Geraldine
gerryarchup@yahoo.co.in
Department of Animal Science,
School of Life Sciences,
Bharathidasan University,
Tiruchirappalli-620024,
Tamilnadu, India

Prabal K. Maiti
maiti@physics.iisc.ernet.in
Centre for Condensed Matter
Theory,
Department of Physics,
Indian Institute of Science,
Bangalore
560012, India

Prasanta K. Nandi
nandi_pk@yahoo.co.in
Department of Chemistry,
Indian Institute of Engineering
Science and Technology,
Shibpur, Howrah, 711103, India

Qingzhong Li
liqingzhong1990@sina.com
The Laboratory of Theoretical and
Computational Chemistry,
School of Chemistry and Chemical
Engineering,
Yantai University, Yantai, 264005,
People's Republic of China

Rafael Najmanovich
rafael.najmanovich@usherbrooke.ca
Department of Biochemistry,
Faculty of Medicine and Health
Sciences,
University of Sherbrooke, 12e
Avenue Nord,
Sherbrooke, J1H 5N4 Québec,
Canada

Rainer A. Böckmann
rainer.boeckmann@fau.de
Computational Biology,
Department of Biology,
Friedrich-Alexander Universität
Erlangen-Nürnberg,
Erlangen, Germany

Roman G. Efremov
r-efremov@yandex.ru
M. M. Shemyakin and Yu. A.
Ovchinnikov Institute of
Bioorganic Chemistry,

Russian Academy of Sciences,
Miklukho-Maklaya Str., 16/10,
Moscow 117997, Russia

Ron Elber
ron@ices.utexas.edu
Department of Chemistry and
the Institute for Computational
Engineering and Sciences,
University of Texas at Austin,
Austin, Texas 78712, United States

Russ B. Altman
russ.altman@stanford.edu
Department of Bioengineering,
Stanford University, 443 Via
Ortega,
Stanford, California 94305-4145,
United States

S. Banu Ozkan
banu.ozkan@asu.edu
Department of Physics and Center
for Biological Physics,
Arizona State University, Tempe,
Arizona

Saeedreza Emamian
saeedreza_em@yahoo.com
Chemistry Department,
Shahrood Branch,
Islamic Azad University,
Shahrood, Iran

Sandip Paul
sandipp@iitg.ernet.in
Department of Chemistry,
Indian Institute of Technology,
Guwahati,
Assam India-781039

Sandro Keller
mail@sandrokeller.com
Molecular Biophysics,
University of Kaiserslautern,
Erwin-Schrödinger-Str. 13,
67663, Kaiserslautern, Germany

Sanjoy Bandyopadhyay
sanjoy@chem.iitkgp.ernet.in
Molecular Modeling Laboratory,
Department of Chemistry,
Indian Institute of Technology,
Kharagpur - 721302, India

Serdar Durdagi
serdar.durdagi@bahcesehir.edu.tr
Department of Biophysics, School
of Medicine,
Bahcesehir University, Istanbul,
Turkey

Sergei F. Vyboishchikov
vyboishchikov@googlemail.com
Departament de Química,
Institut de Química Computacional
i Catàlisi,
Universitat de Girona, Girona,
Spain

Shachi Gosavi
shachi@ncbs.res.in
National Centre for Biological
Sciences,
Tata Institute of Fundamental
Research,
Bellary Road,
Bangalore 560065, India

Sherwin J. Singer
singer@chemistry.ohio-state.edu
Department of Chemistry and
Biochemistry,
The Ohio State University,
Columbus,
Ohio 43210, United States

Shi-Ling Sun, Zhong-Min Su
suns1430@nenu.edu.cn
Institute of Functional Materials
Chemistry,
Faculty of Chemistry, Northeast
Normal University,
Changchun, 130024, Jilin,
Peoples Republic of China

Silmar Andrade do Monte
silmar.monte@uol.com.br
Departamento de Química, CCEN,
Universidade Federal da Paraíba,
João Pessoa, PB, Brazil

Silvia Casassa
silvia.casassa@unito.it
Dipartimento di Chimica,
Università di Torino and NIS,
10125, Italy

Srabani Taraphder
srabani@chem.iitkgp.ernet.in
Department of Chemistry,
Indian Institute of Technology,
Kharagpur
721302, India

Sudip Chattopadhyay
sudip_chattopadhyay@rediffmail.com
Department of Chemistry,
Indian Institute of Engineering
Science and Technology,
Shibpur, Howrah, India

Sukumaran Vasudevan
svipc@ipc.iisc.ernet.in
Department of Inorganic and
Physical Chemistry,
Indian Institute of Science,
Bangalore 560012, India

Suman Kundu
suman.kundu@south.du.ac.in
Department of Biochemistry,
University of Delhi South Campus,
New Delhi, 110021, India.

Supot Hannongbua
supot.h@chula.ac.th

Computational Chemistry Unit
Cell,
Department of Chemistry,
Faculty of Science,
Chulalongkorn University,
Bangkok 10330,
Thailand

Syed Sikander Azam
syedazam2008@gmail.com
Computational Biology Lab,
National Center for Bioinformatics,
Quaid-i-Azam University,
Islamabad 45320, Pakistan

Thomas S. Hofer
T.Hofer@uibk.ac.at
Theoretical Chemistry Division,
Institute of General,
Inorganic and Theoretical
Chemistry
University of Innsbruck,
Innsbruck, Austria

Tomáš Kubař
tomas.kubar@kit.edu
Institute of Physical Chemistry and
Center for Functional
Nanostructures,
Karlsruhe Institute of Technology,
Karlsruhe, Germany

Vanessa Ortiz
vortiz@columbia.edu
Department of Chemical
Engineering,
Columbia University, New York,
New York

Wei Tian
happytw_3000@nwpu.edu.cn
The Key Laboratory of Space
Applied Physics and Chemistry,
Ministry of Education and
Shaanxi Key Laboratory of
Macromolecular Science and
Technology,
School of Science,
Northwestern Polytechnical
University,
Xi'an, 710072, P. R. China

William L. Jorgensen
william.jorgensen@yale.edu
Department of Chemistry,
Yale University, New Haven,
Connecticut

Wonpil Im
wonpil@ku.edu
Department of Molecular
Biosciences and
Center for Computational Biology,
The University of Kansas, 2030
Becker Drive,
Lawrence, Kansas 66047, United
States

Xuechu Zhen, and Wei Fu
zhenxuechu@suda.edu.cn
Jiangsu Key Laboratory for
Translational Research for
Neuropsychiatric-Diseases,
Department of Pharmacology,
College of Pharmaceutical
Sciences,
Soochow University, Suzhou
215123, China

Yanjiang Qiao
yjqiao@263.net
Beijing University of Chinese
Medicine,
Beijing 100102, China

Yingkai Zhang
yingkai.zhang@nyu.edu
Department of Chemistry,
New York University, New York,
New York 10003, United States

Yisheng Lai
yslai@cpu.edu.cn
State Key Laboratory of Natural
Medicines,
Jiangsu Key Laboratory of Drug
Discovery for Metabolic Diseases,
Center of Drug Discovery,
China Pharmaceutical University,
Nanjing 210009, China

Yong Tian
tian_yong_tian@163.com
School of Pharmacy,
Guangdong Pharmaceutical
University,
Guangzhou 510006, Guangdong,
China

Yu Jia
jiayu@zzu.edu.cn
Center for Clean Energy and
Quantum Structures, and
School of Physics and Engineering,
Zhengzhou University, Zhengzhou,
China

Zhong-Min Su
zmsu@nenu.edu.cn
Institute of Functional Material
Chemistry,
Department of Chemistry,
Northeast Normal University,
Changchun, 130024, China

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Editor:

R.Mutyala.
MMCC Results

RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.

David Busath, editor of MMCC Results Volumes 7-14, is Editor Emeritus.

Assistant Editors:

Anston Feenstra, Vrije Univ., Amsterdam, Netherlands

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Synthesis of novel flavone hydrazones: In-vitro evaluation of α -glucosidase inhibition, QSAR analysis and docking studies

Syahrul Imran, Muhammad Taha, Nor Hadiani Ismail [Universiti Teknologi MARA], Syed Muhammad Kashif, Fazal Rahim, Waqas Jamil, Maywan Hariono, Muhammad Yusuf, Habibah Wahab

Eur.Jou. Med. Chem., **103**, 156-170, 2015.

Thirty derivatives of flavone hydrazone (**5–34**) had been synthesized through a five-step reaction and screened for their α -glucosidase inhibition activity. Chalcone **1** was synthesized through aldol condensation then subjected through oxidative cyclization, esterification, and condensation reaction to afford the final products. The result for baker's yeast α -glucosidase (EC 3.2.1.20) inhibition assay showed that all compounds are active with reference to the IC₅₀ value of the acarbose (standard drug) except for compound **3**. Increase in activity observed for compounds **2** to **34** clearly highlights the importance of flavone, hydrazide and hydrazone linkage in suppressing the activity of α -glucosidase.

Discovery and Optimization of Novel, Selective Histone Methyltransferase SET7 Inhibitors by Pharmacophore- and Docking-Based Virtual Screening

Fanwang Meng, Sufang Cheng, Hong Ding, Shien Liu, Yan Liu, Kongkai Zhu, Shijie Chen, Junyan Lu, Yiqian Xie, Linjuan Li, Rongfeng Liu, Zhe Shi, Yu Zhou, Yu-Chih Liu, Mingyue Zheng, Hualiang Jiang, Wencong Lu, Hong Liu, and Cheng Luo [Shanghai Institute of Materia Medica]

J.Med.Chem., **58**, 8166–8181, 2015.

Histone methyltransferases are involved in various biological functions, and these methylation regulating enzymes' abnormal expression or activity has been noted in several human cancers. Within this context, SET domain-containing (lysine methyltransferase) 7 (SET7, also called KMT7, SETD7, SET9) is of increasing significance due to its diverse roles in biological functions and diseases, such as diabetes, cancers, alopecia areata, atherosclerotic vascular disease, HIV, and HCV. In this study, DC-S100, which was discovered by pharmacophore- and docking-based virtual screening, was identified as the hit compound of SET7 inhibitor. Structure–activity relationship (SAR) analysis was performed on analogs of DC-S100 and according to the putative binding mode of DC-S100, structure modifications were made to improve its activity.



MMCC Results

8013 Los Sabalos Street
San Diego, CA 92126
Tel. (858) 663-0162
e-mail: mmccresults@gmail.com

Dr. R. Mutyala.
RR Labs Inc., 8013 Los Sabalos St.
San Diego, CA 92126
Editors Emeritus: Bruce Gelin, Ph.D.
David Busath, M.D.

Dr. Gelin was founder of MMCC Results and edited volumes 1-6.
Dr. David Busath edited volumes 7-14

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Assistant Editors:

Sowmya .N
Rational Labs, Hyderabad., India
Sambasivareddy M
RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of β -Lapachone Analogs as Novel MALT1 Inhibitors To Treat an Aggressive Subtype of Diffuse Large B-Cell Lymphoma

Sang Min Lim, Yujeong Jeong, Suhyun Lee, Honggu Im, Hyun Seop Tae, Byung Gyu Kim, Hee Dong Park, Jonghoon Park, and Sungwoo Hong [Institute of Basic Science (IBS), Daejeon]

J. Med. Chem., **58**, 8491–8502, 2015.

The treatment of activated B cell-like DLBCL (ABC-DLBCL) is one of the urgent unmet medical needs because it is the most resistant DLBCL subtype to current therapies eagerly awaiting effective therapeutic strategies. Recently, the paracaspase MALT1 has emerged as a promising therapeutic target for the treatment of ABC-DLBCL. Herein, we report a new class of MALT1 inhibitors developed by high-throughput screening and structure-based drug design. The original hit, 4-amino-1,2-naphthoquinone series inhibited MALT1 activity but suffered from poor cellular activity. The extensive pharmacophore search led to the discovery of structurally similar β -lapachone that is a direct inhibitor of MALT1 and possesses favorable physicochemical properties.

Sterols and triterpenoids as potential anti-inflammatories: Molecular docking studies for binding to some enzymes involved in inflammatory pathways

Marco A. Loza-Mejía, Juan Rodrigo Salazar [Universidad La Salle]

J. Mol. Graph. and Mod., **62**, 18-25, 2015.

Triterpenes and sterols are good candidates for the development of anti-inflammatory drugs and use in chemoprevention or chemotherapy of cancer via the interaction with therapeutic targets related to inflammation, such as COX-1 and -2; LOX-5; MPO, PLA2 and i-NOS. In this study, we use molecular docking to evaluate the potential binding of a database of selected sterol and triterpenoid compounds with several skeletons against enzymes related to inflammation to propose structural requirements beneficial for anti-inflammatory activity that can be used for the design of more potent and selective anti-inflammatory and antitumor drugs.

Anti-tubercular drug development: computational strategies to identify potential compounds

Sanchaita Rajkhowa, Anupam Nath Jha, Ramesh Chandra Deka [Tezpur University, Napaam]

J. Mol. Graph. and Mod., **62**, 56-68, 2015.

InhA is an attractive target to combat tuberculosis (TB), which is targeted by many pro-drugs (isoniazid, etc.) and drugs such as triclosan. However, triclosan is less useful as an antitubercular drug due to its low bioavailability and therefore, in order to overcome this difficulty, many derivatives of triclosan were prepared. Here, we have combined various computational techniques to virtually screen out four potential triclosan derivatives. Molecular docking methods have been employed to screen out 32 out of 62 triclosan derivatives considering the mode of binding and the top re-rank scores. A comparative study on the chemical properties of triclosan and some of its derivatives has been performed using DFT calculations.

Repurposing Registered Drugs as Antagonists for Protease-Activated Receptor 2

Weijun Xu, Junxian Lim, Chai-Yeen Goh, Jacky Y. Suen, Yuhong Jiang, Mei-Kwan Yau, Kai-Chen Wu, Ligong Liu, and David P. Fairlie [The University of Queensland, Brisbane]

J. Chem. Infor. and Mod. **55**, 2079–2084, 2015.

Virtual screening of a drug database identified Carvedilol, Loratadine, Nefazodone and Astemizole as PAR2 antagonists, after ligand docking and molecular dynamics simulations using a PAR2 homology model and a putative binding mode of a known PAR2 ligand. The drugs demonstrated competitive binding and antagonism of calcium mobilization and ERK1/2 phosphorylation in CHO-hPAR2 transfected cells, while inhibiting IL-6 secretion in PAR2 expressing MDA-MB-231 breast cancer cells.

Medicinal Chemistry and Drug Design (Cont'd)

Elucidation of the binding mechanism of renin using a wide array of computational techniques and biological assays

Haralambos Tzoupis, Georgios Leonis, Aggelos Avramopoulos, Heribert Reis, Żaneta Czyżnikowska, Sofia Zerva, Niki Vergadou, Loukas D. Peristeras, Konstantinos D. Papavasileiou, Michael N. Alexis, Thomas Mavromoustakos, Manthos G. Papadopoulos [National Hellenic Research Foundation]

J. Mol.Graph. and Mod., **62**, 138-149 , 2015.

We investigate the binding mechanism in renin complexes, involving three drugs (remikiren, zankiren and enalkiren) and one lead compound, which was selected after screening the ZINC database. For this purpose, we used ab initio methods (the effective fragment potential, the variational perturbation theory, the energy decomposition analysis, the atoms-in-molecules), docking, molecular dynamics, and the MM-PBSA method. A biological assay for the lead compound has been performed to validate the theoretical findings. Importantly, binding free energy calculations for the three drug complexes are within 3 kcal/mol of the experimental values, thus further justifying our computational protocol, which has been validated through previous studies on 11 drug-protein systems.

Evaluation of novel Akt1 inhibitors as anticancer agents using virtual co-crystallized pharmacophore generation

Mahmoud A. Al-Sha'er [Zarqa University], Iman Mansi, Inas Almazari, Nancy Hakooz

J. Mol.Graph. and Mod., **62**, 213-225, 2015.

The pharmacophoric features of the virtual co-crystallized protein of 17 Akt1 proteins were downloaded from the protein data bank, and explored to end up with 132 generated pharmacophores that had been evaluated using the decoy list composed of 1724 compounds. The areas under the curve of the Receiver-Operating Characteristic (ROC-AUC) were sorted, and the highest ranked pharmacophore **3MV5_2_01** was selected to be used as a searching tool in the National Cancer Institute (NCI) database. The captured hits were mapped based on successful hypotheses and the best fitted compounds were selected.

Structure-based de novo design, molecular docking and molecular dynamics of primaquine analogues acting as quinone reductase II inhibitors

Erika Murce, Teobaldo Ricardo Cuya-Guizado, Helmut Isaac Padilla-Chavarria, Tanos Celmar Costa França, Andre Silva Pimentel [Pontifícia Universidade Católica do Rio de Janeiro]

J. Mol.Graph. and Mod., **62**, 235-244 , 2015.

Primaquine is a traditional antimalarial drug with low parasitic resistance and generally good acceptance at higher doses, which has been used for over 60 years in malaria treatment. However, several limitations related to its hematotoxicity have been reported. It is believed that this toxicity comes from the hydroxylation of the C-5 and C-6 positions of its 8-aminoquinoline ring before binding to the molecular target: the quinone reductase II (NQO2) human protein. In this study we propose primaquine derivatives, with substitution at position C-6 of the 8-aminoquinoline ring, planned to have better binding to NQO2, compared to primaquine, but with a reduced toxicity related to the C-5 position being possible to be oxidized.

Medicinal Chemistry and Drug Design (Cont'd)

An ab initio molecular dynamics analysis of lignin as a potential antioxidant for hydrocarbons

Tongyan Pan, Cheng Cheng [Illinois Institute of Technology]

J. Mol.Graph. and Mod., **62**, 325-341 , 2015.

Lignins are complex phenolic polymers with limited industrial uses. To identify new applications of lignins, this study aims to evaluate the conifer alcohol lignin as a potential antioxidant for hydrocarbons, using the petroleum asphalt as an example. Using the ab initio molecular dynamics (AIMD) method, the evaluation is accomplished by tracking the generation of critical species in a lignin-asphalt mixture under a simulated oxidative condition. The generation of new species was detected using nuclear magnetic resonance and four analytical methods including density of states analysis, highest occupied molecular orbital and lowest unoccupied molecular orbital analyses, bonding and energy level analysis, and electrostatic potential energy analysis.

Functional insights from a comparative study on the dynamics of Antigen85 proteins and MPT51 from Mycobacterium tuberculosis

Shobana Sundar, David Annaraj, Anitha Selvan, Pallavi Guha Biswas, Reshma Vijayakumaran, Sharmila Anishetty [Anna University, Chennai]

J. Mol.Mod., **21**, 310, 2015.

Antigen85 (Ag85) proteins of Mycobacterium tuberculosis are mycolyl transferases that aid in cell wall biosynthesis. MPT51 (Ag85D) is closely related to Ag85 proteins. We have performed a comparative molecular dynamics (MD) simulation study of Ag85 proteins (Ag85A, Ag85B, and Ag85C) and MPT51. We observe that helix $\alpha 5$, $\beta 7$ - $\alpha 9$ loop, and N-terminal region of helix $\alpha 9$ of Ag85 proteins are mobile, suggestive of lid like movement over the active site. Further, in Ag85B, we observe the proposed scooting mode of the hydrophobic gating residue Phe232. Our simulations also show a similar scooting mode for Phe232 of Ag85A and Trp158 of Ag85C.

Ligand-Based Virtual Screening in a Search for Novel Anti-HIV-1 Chemotypes

Agata Kurczyk, Dawid Warszycki, Robert Musiol, Rafał Kafel, Andrzej J. Bojarski, and Jaroslaw Polanski [University of Silesia]

J.Chem. Infor. and Mod. **55**, 2168–2177, 2015.

In a search for new anti-HIV-1 chemotypes, we developed a multistep ligand-based virtual screening (VS) protocol combining machine learning (ML) methods with the privileged structures (PS) concept. In its learning step, the VS protocol was based on HIV integrase (IN) inhibitors fetched from the ChEMBL database. The performances of various ML methods and PS weighting scheme were evaluated and applied as VS filtering criteria. Finally, a database of 1.5 million commercially available compounds was virtually screened using a multistep ligand-based cascade, and 13 selected unique structures were tested by measuring the inhibition of HIV replication in infected cells.

Medicinal Chemistry and Drug Design (Cont'd)

Exploring interaction mechanisms of the inhibitor binding to the VP35 IID region of Ebola virus by all atom molecular dynamics simulation method

Yan-Jun Zhang, Jing-Na Ding, Ting-Ting Feng and Ju-Guang Han [University of Science and Technology of China]

Proteins: Stru. Fun. & Bioinf., **83**, 2263–2278, 2015.

Ebola viruses (EBOVs) cause an acute and serious illness which is often fatal if untreated, and there is no effective vaccine until now. Multifunctional VP35 is critical for viral replication, RNA silencing suppression and nucleocapsid formation, and it is considered as a future target for the molecular biology technique. In the present work, the binding of inhibitor pyrrole-based compounds (GA017) to wild-type (WT), single (K248A, K251A, and I295A), and double (K248A/I295A) mutant VP35 were investigated by all-atom molecular dynamic (MD) simulations and Molecular Mechanics Generalized Born surface area (MM/GBSA) energy calculation.

Conformational variation of an extreme drug resistant mutant of HIV protease

Chen-Hsiang Shen, Yu-Chung Chang, Johnson Agniswamy, Robert W. Harrison, Irene T. Weber [Georgia State University]

J. Mol.Graph. and Mod., **62**, 87-96, 2015.

Molecular mechanisms leading to high level drug resistance have been analyzed for the clinical variant of HIV-1 protease bearing 20 mutations (PR20); which has several orders of magnitude worse affinity for tested drugs. Two crystal structures of ligand-free PR20 with the D25N mutation of the catalytic aspartate (PR20_{D25N}) revealed three dimers with different flap conformations. The diverse conformations of PR20_{D25N} included a dimer with one flap in a unique “tucked” conformation; directed into the active site. Analysis of molecular dynamics (MD) simulations of the ligand-free PR20 and wild-type enzymes showed that the mutations in PR20 alter the correlated interactions between two monomers in the dimer.

Carbon Nanoparticles

Coarse-grained molecular dynamics simulation of water diffusion in the presence of carbon nanotubes

Isabel Lado Touriño, Arisbel Cerpa Naranjo, Viviana Negri, Sebastián Cerdán, Paloma Ballesteros [Faculty of Sciences, UNED]

J. Mol.Graph. and Mod., **62**, 69-73, 2015.

Computational modeling of the translational diffusion of water molecules in anisotropic environments entails vital relevance to understand correctly the information contained in the magnetic resonance images weighted in diffusion (DWI) and of the diffusion tensor images (DTI). In the present work we investigated the validity, strengths and weaknesses of a coarse-grained (CG) model based on the MARTINI force field to simulate water diffusion in a medium containing carbon nanotubes (CNTs) as models of anisotropic water diffusion behavior. We show that water diffusion outside the nanotubes follows Fick's law, while water diffusion inside the nanotubes is not described by a Fick's behavior.

1.2. Biopolymers

Bioinformatics and Cheminformatics

ProFET: Feature engineering captures high-level protein functions

Dan Ofer and Michal Linial [The Hebrew University of Jerusalem]

Bioinformatics. **31**, 3429-3436, 2015.

The amount of sequenced genomes and proteins is growing at an unprecedented pace. Unfortunately, manual curation and functional knowledge lag behind. Homologous inference often fails at labeling proteins with diverse functions and broad classes. In this study, we present a novel bioinformatics toolkit called ProFET (Protein Feature Engineering Toolkit). ProFET extracts hundreds of features covering the elementary biophysical and sequence derived attributes. Most features capture statistically informative patterns. In addition, different representations of sequences and the amino acids alphabet provide a compact, compressed set of features.

TEtranscripts: a package for including transposable elements in differential expression analysis of RNA-seq datasets

Ying Jin, Oliver H. Tam, Eric Paniagua, and Molly Hammell [Cold Spring Harbor Laboratory]

Bioinformatics. **31**, 3593-3599, 2015.

Most RNA-seq data analysis software packages are not designed to handle the complexities involved in properly apportioning short sequencing reads to highly repetitive regions of the genome. These regions are often occupied by transposable elements (TEs), which make up between 20 and 80% of eukaryotic genomes. Here, we present a method and software package for including both gene- and TE-associated ambiguously mapped reads in differential expression analysis. Our method shows improved recovery of TE transcripts over other published expression analysis methods, in both synthetic data and qPCR/NanoString-validated published datasets.

MONA 2: A Light Cheminformatics Platform for Interactive Compound Library Processing

Matthias Hilbig and Matthias Rarey [University of Hamburg]

J.Chem. Infor. and Mod. **55**, 2071–2078, 2015.

Because of the availability of large compound collections on the Web, elementary cheminformatics tasks such as chemical library browsing, analyzing, filtering, or unifying have become widespread in the life science community. Furthermore, the high performance of desktop hardware allows an interactive, problem-driven approach to these tasks, avoiding rigid processing scripts and workflows. Here, we present MONA 2, which is the second major release of our cheminformatics desktop application addressing this need.

PyEMMA 2: A Software Package for Estimation, Validation, and Analysis of Markov Models

Martin K. Scherer, Benjamin Trendelkamp-Schroer, Fabian Paul, Guillermo Pérez-Hernández, Moritz Hoffmann, Nuria Plattner, Christoph Wehmeyer, Jan-Hendrik Prinz, and Frank Noé [Freie Universität]

J. Chem. Theor. and Comp. **11**, 5525–5542, 2015.

Markov (state) models (MSMs) and related models of molecular kinetics have recently received a surge of interest as they can systematically reconcile simulation data from either a few long or many short simulations and allow us to analyze the essential metastable structures, thermodynamics, and kinetics of the molecular system under investigation. . In this work we present the open-source Python package PyEMMA (<http://pyemma.org>) that provides accurate and efficient algorithms for kinetic model construction.

Protein Structure Prediction

Partial unfolding and refolding for structure refinement: A unified approach of geometric simulations and molecular dynamics

Avishek Kumar, Paul Campitelli, M. F. Thorpe and S. Banu Ozkan [Arizona State University, Tempe]

Proteins: Stru. Fun. & Bioinf., **83**, 2279–2292, 2015.

The most successful protein structure prediction methods to date have been template-based modeling (TBM) or homology modeling, which predicts protein structure based on experimental structures. These high accuracy predictions sometimes retain structural errors due to incorrect templates or a lack of accurate templates in the case of low sequence similarity, making these structures inadequate in drug-design studies or molecular dynamics simulations. We have developed a new physics based approach to the protein refinement problem by mimicking the mechanism of chaperons that rehabilitate misfolded proteins.

Comparative or Homology Modeling

Comparison of templates for homology model of $\rho 1$ GABA_C receptors: More insights to the orthosteric binding site's structure and functionality

Moawiah M Naffaa, Mary Chebib, David E Hibbs, Jane R Hanrahan [University of Sydney]

J. Mol.Graph. and Mod., **62**, 43-55, 2015.

Five sets of $\rho 1$ GABA_C homology models were generated based on X-ray crystal structures of the acetylcholine binding protein (AChBP), the ion channel from *Caenorhabditis elegans* (GLIC), the ion channel from *Erwinia chrysanthemi* (ELIC), the homomeric GABA_A β_3 ion channel, and the homomeric α -subunit of glutamate-gated homopentameric chloride channel (GluCl). The GluCl based model was found to represent the structure of $\rho 1$ GABA_C receptors. The GABA pose docked in the selected best model was confirmed by QM-polarized ligand docking and induced fit docking protocol, and used to study molecular interactions in the $\rho 1$ GABA binding site.

Homology modeling of parasite histone deacetylases to guide the structure-based design of selective inhibitors

Jelena Melesina, Dina Robaa, Raymond J. Pierce, Christophe Romier, Wolfgang Sippl [Martin-Luther-Universität Halle-Wittenberg]

J. Mol.Graph. and Mod., **62**, 342-361 , 2015.

Histone deacetylases (HDACs) are promising epigenetic targets for the treatment of various diseases, including cancer and neurodegenerative disorders. There is evidence that they can also be addressed to treat parasitic infections. Recently, the first X-ray structure of a parasite HDAC was published, *Schistosoma mansoni* HDAC8, giving structural insights into its inhibition. However, most of the targets from parasites of interest still lack this structural information. Therefore, we prepared homology models of relevant parasitic HDACs and compared them to human and *S. mansoni* HDACs.

Protein Conformational Analysis

Molecular dynamics study of the effect of active site protonation on *Helicobacter pylori* 5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase

Mustafa Tekpınar [Yüzüncü Yıl University], Ahmet Yıldırım, Tsjerk A. Wassenaar

Eur. Biophys., 44, 685-696, 2015.

The protein 5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase (MTAN) is involved in the quorum sensing of several bacterial species, including *Helicobacter pylori*. In particular, these bacteria depend on MTAN for synthesis of vitamin K₂ homologs. The residue D198 in the active site of MTAN seems to be of crucial importance, by acting as a hydrogen-bond acceptor for the ligand. In this study, we investigated the conformation and dynamics of apo and holo *H. pylori* MTAN (HpMTAN), and assessed the effect of protonation of D198 by use of molecular dynamics simulations.

Toward Focusing Conformational Ensembles on Bioactive Conformations: A Molecular Mechanics/Quantum Mechanics Study

Hannah H. Avgy-David and Hanoch Senderowitz [Bar Ilan University]

J. Chem. Infor. and Mod. 55, 2154–2167, 2015.

The identification of bound conformations, namely, conformations adopted by ligands when binding their target is critical for target-based and ligand-based drug design. Bound conformations could be obtained computationally from unbound conformational ensembles generated by conformational search tools. However, these tools also generate many nonrelevant conformations thus requiring a focusing mechanism. To identify such a mechanism, this work focuses on a comparison of energies and structural properties of bound and unbound conformations for a set of FDA approved drugs whose complexes are available in the PDB.

Nontargeted Parallel Cascade Selection Molecular Dynamics for Enhancing the Conformational Sampling of Proteins

Ryuhei Harada and Akio Kitao [University of Tsukuba]

J. Chem. Theor. and Comp. 11, 5493–5502, 2015.

Nontargeted parallel cascade selection molecular dynamics (nt-PaCS-MD) is proposed as an efficient conformational sampling method to enhance the conformational transitions of proteins, which is an extension of the original targeted PaCS-MD (t-PaCS-MD). The original PaCS-MD comprises cycles of (i) selection of initial structures for multiple independent MD simulations toward a predetermined target and (ii) conformational sampling by the independent MDs. In nt-PaCS-MD, structures that significantly deviate from an average are regarded as candidates that have high potential to address other metastable states and are chosen as the initial structures in the selection.

Internal Normal Mode Analysis (iNMA) Applied to Protein Conformational Flexibility

Elisa Frezza and Richard Lavery [Institut de Biologie et Chimie des Protéines]

J. Chem. Theor. and Comp. 11, 5503–5512, 2015.

We analyze the capacity of normal modes to predict observed protein conformational changes, and, notably, those induced by the formation of protein–protein complexes. We show that normal modes calculated in internal coordinate space (ICS) provide better predictions. For a large test set, using the ICS approach describes the conformational changes more completely, and with fewer low-frequency modes than the equivalent Cartesian coordinate modes, despite the fact that the internal coordinate calculations were restricted to torsional angles.

Protein Conformational Analysis (Cont'd)

Avalanche for shape and feature-based virtual screening with 3D alignment

David J. Diller, Nancy D. Connell, William J. Welsh [Rutgers University, Piscataway]

J. Comp. Aided. Mol. des. **29**, 1015-1024, 2015.

This report introduces a new ligand-based virtual screening tool called Avalanche that incorporates both shape- and feature-based comparison with three-dimensional (3D) alignment between the query molecule and test compounds residing in a chemical database. Avalanche proceeds in two steps. The first step is an extremely rapid shape/feature based comparison which is used to narrow the focus from potentially millions or billions of candidate molecules and conformations to a more manageable number that are then passed to the second step. The second step is a detailed yet still rapid 3D alignment of the remaining candidate conformations to the query conformation.

Effects of the C-Terminal Tail on the Conformational Dynamics of Human Neuronal Calcium Sensor-1 Protein

Yuzhen Zhu, Shuang Yang, Ruxi Qi, Yu Zou, Buyong Ma, Ruth Nussinov, and Qingwen Zhang [Shanghai University of Sport]

J. Phys. Chem. B., **119**, 14236–14244, 2015.

Neuronal calcium sensor-1 (NCS-1) protein has been implicated in multiple neuronal functions by binding partners mostly through a largely exposed hydrophobic crevice (HC). In the absence of a ligand, the C-terminal tail (loop L3, residues D176 to V190) binds directly to the HC pocket as a ligand mimetic, occupying the HC and regulating its conformational stability. A recent experimental study reported that L3 deletion resulted in global structure destabilization. In this study, we investigated the structural properties and the conformational dynamics of wild type NCS-1 and L3 truncation variant by extensive all-atom molecular dynamics (MD) simulations.

Domain Motion Enhanced (DoME) Model for Efficient Conformational Sampling of Multidomain Proteins

Chigusa Kobayashi, Yasuhiro Matsunaga, Ryotaro Koike, Motonori Ota, and Yuji Sugita [RIKEN Advanced Institute for Computational Science]

J. Phys. Chem. B., **119**, 14584–14593, 2015.

Large conformational changes of multidomain proteins are difficult to simulate using all-atom molecular dynamics (MD) due to the slow time scale. We show that a simple modification of the structure-based coarse-grained (CG) model enables a stable and efficient MD simulation of those proteins. “Motion Tree”, a tree diagram that describes conformational changes between two structures in a protein, provides information on rigid structural units (domains) and the magnitudes of domain motions. In our new CG model, which we call the DoME (domain motion enhanced) model, interdomain interactions are defined as being inversely proportional to the magnitude of the domain motions in the diagram, whereas intradomain interactions are kept constant.

Protein Conformational Analysis (Cont'd)

Toward an Enhanced Sampling Molecular Dynamics Method for Studying Ligand-Induced Conformational Changes in Proteins

Ole Juul Andersen, Julie Grouleff, Perri Needham, Ross C. Walker, and Frank Jensen [Aarhus University]

J. Phys. Chem. B., **119**, 14594–14603, 2015.

Current enhanced sampling molecular dynamics methods for studying large conformational changes in proteins suffer from certain limitations. These include, among others, the need for user defined collective variables, the prerequisite of both start and end point structures of the conformational change, and the need for a priori knowledge of the amount by which to boost specific parts of the potential. In this paper, a framework is proposed for a molecular dynamics method for studying ligand-induced conformational changes, in which the nonbonded interactions between the ligand and the protein are used to calculate a biasing force.

Pressure-induced structural transition of mature HIV-1 protease from a combined NMR/MD simulation approach

Julien Roche, John M. Louis, Ad Bax and Robert B. Best [National Institutes of Health, Bethesda]

Proteins: Stru. Fun. & Bioinf., **83**, 2117–2123, 2015.

We investigate the pressure-induced structural changes in the mature human immunodeficiency virus type 1 protease dimer, using residual dipolar coupling (RDC) measurements in a weakly oriented solution. $^1\text{D}_{\text{NH}}$ RDCs were measured under high-pressure conditions for an inhibitor-free PR and an inhibitor-bound complex, as well as for an inhibitor-free multidrug resistant protease bearing 20 mutations (PR20). While PR20 and the inhibitor-bound PR were little affected by pressure, inhibitor-free PR showed significant differences in the RDCs measured at 600 bar compared with 1 bar.

Shortening a loop can increase protein native state entropy

Yulian Gavrilov, Shlomi Dagan and Yaakov Levy [Weizmann Institute of Science]

Proteins: Stru. Fun. & Bioinf., **83**, 2137–2146, 2015.

Protein loops are essential structural elements that influence not only function but also protein stability and folding rates. It was recently reported that shortening a loop in the AcP protein may increase its native state conformational entropy. This effect on the entropy of the folded state can be much larger than the lower entropic penalty of ordering a shorter loop upon folding, and can therefore result in a more pronounced stabilization than predicted by polymer model for loop closure entropy. In this study, which aims at generalizing the effect of loop length shortening on native state dynamics, we use all-atom molecular dynamics simulations to study how gradual shortening a very long or solvent-exposed loop region in four different proteins can affect their stability.

Protein Dynamics

WATCLUST: a tool for improving the design of drugs based on protein-water interactions

Elias D. López, Juan Pablo Arcon, Diego F. Gauto, Ariel A. Petruk, Carlos P. Modenutti, Victoria G. Dumas, Marcelo A. Marti, and Adrian G. Turjanski [Universidad de Buenos Aires]

Bioinformatics. **31**, 3697-3699, 2015.

Water molecules are key players for protein folding and function. On the protein surface, water is not placed randomly, but display instead a particular structure evidenced by the presence of specific water sites (WS). These WS can be derived and characterized using explicit water MD simulations, providing useful information for ligand binding prediction and design. We present WATCLUST, a WS determination and analysis tool running on the VMD platform. The tool also allows direct transfer of the WS information to Autodock program to perform biased docking.

Discovery and Characterization of a Peptide That Enhances Endosomal Escape of Delivered Proteins In Vitro and in Vivo

Margie Li, Yong Tao, Yilai Shu, Jonathan R. LaRochelle, Angela Steinauer, David Thompson, Alanna Schepartz, Zheng-Yi Chen, and David R. Liu [Harvard University]

J. Am. Chem. Soc., **137**, 14084–14093, 2015.

The inefficient delivery of proteins into mammalian cells remains a major barrier to realizing the therapeutic potential of many proteins. We and others have previously shown that superpositively charged proteins are efficiently endocytosed and can bring associated proteins and nucleic acids into cells. The vast majority of cargo delivered in this manner, however, remains in endosomes and does not reach the cytosol. In this study we designed and implemented a screen to discover peptides that enhance the endosomal escape of proteins fused to superpositively charged GFP (+36 GFP).

PrinCCes: Continuity-based geometric decomposition and systematic visualization of the void repertoire of proteins

Gábor Czirják [Simmelweis University]

J. Mol.Graph. and Mod., **62**, 118-127, 2015.

Grooves and pockets on the surface, channels through the protein, the chambers or cavities, and the tunnels connecting the internal points to each other or to the external fluid environment are fundamental determinants of a wide range of biological functions. PrinCCes (Protein internal Channel & Cavity estimation) is a computer program supporting the visualization of voids. It includes a novel algorithm for the decomposition of the entire void volume of the protein or protein complex to individual entities. The decomposition is based on continuity.

An investigation of folic acid–protein association sites and the effect of this association on folic acid self-assembly

Rajat Gupta, Prasanta Kalita, Omkar Patil, Sanat Mohanty [Indian Institute of Technology Delhi]

J. Mol.Mod., **21**, 308, 2015.

The contribution of folic acid (FA)–tryptophan interactions to FA–protein association was investigated in the context of using FA as a drug carrier in protein delivery systems. Bovine serum albumin (BSA) and indolicidin were used as model proteins in the study. The FA-BSA complex was characterized by using the Bradford reagent to identify the impact of FA-BSA association on BSA–dye reagent interactions. UV-visible spectroscopic analysis of the FA–BSA mixture showed that the absorbance maximum of BSA–dye reagent occurred at 595 nm, even after the association of FA with BSA.

Protein Dynamics (Cont'd)

Structural and Dynamic Characterization of Mutated Keap1 for Varied Affinity toward Nrf2: A Molecular Dynamics Simulation Study

I-Chung Cheng, Ya-Jyun Chen, Chia-Wei Ku, Yu-Wen Huang, and Chia-Ning Yang [National University of Kaohsiung]

J.Chem. Infor. and Mod. **55**, 2178–2186, 2015.

Keap1 is an adaptor protein that regulates Nrf2 in response to oxidative stress. Under basal conditions, Nrf2 is negatively regulated through ubiquitination by Keap1. However, upon exposure to oxidative stress, the ubiquitination of Nrf2 is inhibited, resulting in an increased steady-state level of Nrf2 in the nucleus and increased transcription of cytoprotective genes. A gene variant G364C and somatic mutation G430C on Keap1 have recently been reported to substantially impair the Keap1–Nrf2 interaction and to be associated with lung cancer. In this study, molecular dynamics simulations were performed to investigate the structural and dynamic variances among wild-type (WT) Keap1 and the six mutants in unbound form.

Folding Thermodynamics and Mechanism of Five Trp-Cage Variants from Replica-Exchange MD Simulations with RSFF2 Force Field

Chen-Yang Zhou, Fan Jiang, and Yun-Dong Wu [Peking University Shenzhen Graduate School]

J. Chem. Theor. and Comp. **11**, 5473–5480, 2015.

To test whether our recently developed residue-specific force field RSFF2 can reproduce the mutational effect on the thermal stability of Trp-cage mini-protein and decipher its detailed folding mechanism, we carried out long-time replica-exchange molecular dynamics (REMD) simulations on five Trp-cage variants, including TC5b and TC10b. Initiated from their unfolded structures, the simulations not only well-reproduce their experimental structures but also their melting temperatures and folding enthalpies reasonably well.

Structural Ensembles of Intrinsically Disordered Proteins Depend Strongly on Force Field: A Comparison to Experiment

Sarah Rauscher [Max Planck Institute for Biophysical Chemistry], Vytautas Gapsys, Michal J. Gajda, Markus Zweckstetter, Bert L. de Groot, and Helmut Grubmüller

J. Chem. Theor. and Comp. **11**, 5513–5524, 2015.

Intrinsically disordered proteins (IDPs) are notoriously challenging to study both experimentally and computationally. The structure of IDPs cannot be described by a single conformation but must instead be described as an ensemble of interconverting conformations. Atomistic simulations are increasingly used to obtain such IDP conformational ensembles. Here, we have compared the IDP ensembles generated by eight all-atom empirical force fields against primary small-angle X-ray scattering (SAXS) and NMR data. Ensembles obtained with different force fields exhibit marked differences in chain dimensions, hydrogen bonding, and secondary structure content.

Empirical Optimization of Interactions between Proteins and Chemical Denaturants in Molecular Simulations

Wenwei Zheng, Alessandro Borgia, Madeleine B. Borgia, Benjamin Schuler, and Robert B. Best [National Institutes of Health, Bethesda]

J. Chem. Theor. and Comp. **11**, 5543–5553, 2015.

Chemical denaturants are the most commonly used perturbation applied to study protein stability and folding kinetics as well as the properties of unfolded polypeptides. We build on recent work balancing the interactions of proteins and water, and accurate models for the solution properties of urea and guanidinium chloride, to develop a combined force field that is able to capture the strength of interactions between proteins and denaturants. We use solubility data for a model tetraglycine peptide in each denaturant to tune the protein–denaturant interaction by a novel simulation methodology.

Protein Dynamics (Cont'd)

Diffusion of Hydration Water around Intrinsically Disordered Proteins

Pooja Rani and Parbati Biswas [University of Delhi]

J. Phys. Chem. B., **119**, 13262–13270, 2015.

Hydration water dynamics around globular proteins have attracted considerable attention in the past decades. This work investigates the hydration water dynamics around partially/fully intrinsically disordered proteins and compares it to that of the globular proteins via molecular dynamics simulations. The translational diffusion of the hydration water is examined by evaluating the mean-square displacement and the velocity autocorrelation function, while the rotational diffusion is probed through the dipole–dipole time correlation function.

Sequence- and Temperature-Dependent Properties of Unfolded and Disordered Proteins from Atomistic Simulations

Gül H. Zerze, Robert B. Best, and Jeetain Mittal [Lehigh University, Bethlehem]

J. Phys. Chem. B., **119**, 14622–14630, 2015.

We use all-atom molecular simulation with explicit solvent to study the properties of selected intrinsically disordered proteins and unfolded states of foldable proteins, which include chain dimensions and shape, secondary structure propensity, solvent accessible surface area, and contact formation. We find that the qualitative scaling behavior of the chains matches expectations from theory under ambient conditions. In particular, unfolded globular proteins tend to be more collapsed under the same conditions than charged disordered sequences of the same length.

An amino acid code for irregular and mixed protein packing

Hyun Joo, Archana G. Chavan, Keith J. Fraga and Jerry Tsai [University of the Pacific]

Proteins: Stru. Fun. & Bioinf., **83**, 2147–2161, 2015.

To advance our understanding of protein tertiary structure, the development of the knob-socket model is completed in an analysis of the packing in irregular coil and turn secondary structure packing as well as between mixed secondary structure. The knob-socket model simplifies packing based on repeated patterns of two motifs: a three-residue socket for packing within secondary (2°) structure and a four-residue knob-socket for tertiary (3°) packing. For coil and turn secondary structure, knob-sockets allow identification of a correlation between amino acid composition and tertiary arrangements in space.

Toward decrypting the allosteric mechanism of the ryanodine receptor based on coarse-grained structural and dynamic modeling

Wenjun Zheng [239 Fronczak Hall, Buffalo]

Proteins: Stru. Fun. & Bioinf., **83**, 2307–2318, 2015.

The ryanodine receptors (RyRs) are a family of calcium (Ca) channels that regulate Ca release by undergoing a closed-to-open gating transition in response to action potential or Ca binding. The allosteric mechanism of RyRs gating, which is activated/regulated by ligand/protein binding >200 Å away from the channel gate, remains elusive for the lack of high-resolution structures. Recent solution of the closed-form structures of the RyR1 isoform by cryo-electron microscopy has paved the way for detailed structure-driven studies of RyRs functions. Toward elucidating the allosteric mechanism of RyRs gating, we performed coarse-grained modeling based on the newly solved closed-form structures of RyR1.

Free Energy Calculations

A Python tool to set up relative free energy calculations in GROMACS

Pavel V. Klimovich, David L. Mobley [University of California, Irvine]

J.Comp.Aided. Mol.des. **29**, 1007-1014, 2015.

Free energy calculations based on molecular dynamics (MD) simulations have seen a tremendous growth in the last decade. However, it is still difficult and tedious to set them up in an automated manner, as the majority of the present-day MD simulation packages lack that functionality. Relative free energy calculations are a particular challenge for several reasons, including the problem of finding a common substructure and mapping the transformation to be applied. Here we present a tool, *alchemical-setup.py*, that automatically generates all the input files needed to perform relative solvation and binding free energy calculations with the MD package GROMACS.

Ligand Binding/Docking

Identification and characterization of a glycosaminoglycan binding site on interleukin-10 via molecular simulation methods

Jan-Philip Gehrcke, M. Teresa Pisabarro [Structural Bioinformatics, BIOTEC]

J. Mol.Graph. and Mod., **62**, 97-104, 2015.

The biological function of the pleiotropic cytokine interleukin-10 (IL-10), which has an essential role in inflammatory processes, is known to be affected by glycosaminoglycans (GAGs). GAGs are essential constituents of the extracellular matrix with an important role in modulating the biological function of many proteins. The molecular mechanisms governing the IL-10–GAG interaction, though, are unclear so far. In the present work, we report a GAG binding site on IL-10 identified by applying computational methods based on Coulomb potential calculations and specialized molecular dynamics simulations.

A ligand-entry surface of the nuclear receptor superfamily consists of the helix H3 of the ligand-binding domain

Motonori Tsuji [Institute of Molecular Function, 2-105-14 Takasu]

J. Mol.Graph. and Mod., **62**, 262-275, 2015.

We successfully simulated receptor-ligand complex holo-form formation using the human retinoid X receptor- α ligand-binding domain (LBD) and its natural ligand, 9-cis retinoic acid. The success of this simulation was strongly dependent on the findings for an initial structure between the apo-LBD and the ligand as well as the discovery of the driving forces underlying the ligand-trapping and subsequent ligand-induction processes. Here, we would like to propose the “helix H3 three-point initial-binding hypothesis,” which was instrumental in simulating the nuclear receptor (NR) superfamily.

Ligand Binding / Docking (Cont'd)

Insights from Fragment Hit Binding Assays by Molecular Simulations

Noelia Ferruz, Matthew J. Harvey, Jordi Mestres, and Gianni De Fabritiis [Universitat Pompeu Fabra]

J.Chem. Infor. and Mod. **55**, 2200–2205, 2015.

Novel bioactive molecules can be rationally designed by growing and linking small fragments. Because fragments are fast and promiscuous, it is common to have contradictory hit results between different experimental screening techniques. Here, we simultaneously determine fragment binding poses, affinities, and kinetics on a focused library of 42 fragments against the serine protease factor Xa using multimillisecond molecular dynamics simulations. We predict experimental poses of 12 over 15 S1 crystal structures, and affinities are recovered for 4 out of 6. A kinetic map of protein cavities is computed in terms of on- and off-rates as well as insights into secondary ligand poses.

Docking simulations suggest that all-trans retinoic acid could bind to retinoid X receptors

Motonori Tsuji [Institute of Molecular Function, 2-105-14 Takasu], Koichi Shudo, Hiroyuki Kagechika

J.Comp.Aided. Mol.des. **29**, 975-988, 2015.

Retinoid X receptors (RXRs) are ligand-controlled transcription factors which heterodimerize with other nuclear receptors to regulate gene transcriptions associated with crucial biological events. 9-cis retinoic acid (9cRA), which transactivates RXRs, is believed to be an endogenous RXR ligand. All-trans retinoic acid (ATRA) is a natural ligand for retinoic acid receptors (RARs), which heterodimerize with RXRs. Although the concentration of 9cRA in tissues is very low, ATRA is relatively abundant and some reports show that ATRA activates RXRs.

Hydration of Caffeine at High Temperature by Neutron Scattering and Simulation Studies

L. Tavagnacco, J. W. Brady, F. Bruni, S. Callear, M. A. Ricci, M. L. Saboungi, and A. Cesàro [University of Trieste]

J. Phys. Chem. B., **119**, 13294–13301, 2015.

The solvation of caffeine in water is examined with neutron diffraction experiments at 353 K. The experimental data, obtained by taking advantage of isotopic H/D substitution in water, were analyzed by empirical potential structure refinement (EPSR) in order to extract partial structure factors and site–site radial distribution functions. In parallel, molecular dynamics (MD) simulations were carried out to interpret the data and gain insight into the intermolecular interactions in the solutions and the solvation process.

Simple Statistical Model for Branched Aggregates: Application to Cooee Bitumen

Claire A. Lemarchand [Roskilde University] and Jesper S. Hansen

J. Phys. Chem. B., **119**, 14323–14331, 2015.

We propose a statistical model that can reproduce the size distribution of any branched aggregate, including amylopectin, dendrimers, molecular clusters of monoalcohols, and asphaltene nanoaggregates. It is based on the conditional probability for one molecule to form a new bond with a molecule, given that it already has bonds with others. The model is applied here to asphaltene nanoaggregates observed in molecular dynamics simulations of Cooee bitumen. The variation with temperature of the probabilities deduced from this model is discussed in terms of statistical mechanics arguments.

Enzyme Catalysis

Binding site identification and role of permanent water molecule of PIM-3 kinase: A molecular dynamics study

Zaheer Ul-Haq [University of Karachi], Sana Gul, Saman Usmani, Abdul Wadood, Waqasuddin Khan

J. Mol.Graph. and Mod., **62**, 276-282 , 2015.

The kinome is a protein kinase complement of the human genome, categorized as serine/threonine and tyrosine kinases. These kinases catalyze phosphorylation reaction by using ATP as phosphoryl donor. Proviral Integration Site for Moloney Murine Leukemia Virus (PIM) kinase encodes serine/threonine protein kinases that recognized as proto-oncogene, responsible for rapid growth of cancerous cells. PIM-3, sub-member of PIM kinases is a proto-oncogene, its overexpression inhibits apoptosis, and results in progression of hepatocellular carcinoma. Here, homology modeling, molecular docking and MD simulation techniques were utilized to explore the structure and dynamics of PIM-3 kinase.

Rational design of a carboxylic esterase RhEst1 based on computational analysis of substrate binding

Qi Chen, Zheng-Jiao Luan, Hui-Lei Yu, Xiaolin Cheng, Jian-He Xu [East China University of Science and Technology]

J. Mol.Graph. and Mod., **62**, 319-324, 2015.

A new carboxylic esterase RhEst1 which catalyzes the hydrolysis of (S)-(+)-2,2-dimethylcyclopropanecarboxylate (S-DmCpCe), the key chiral building block of cilastatin, was identified and subsequently crystallized in our previous work. Mutant RhEst1_{A147I/V148F/G254A} was found to show a 5-fold increase in the catalytic activity. In this work, molecular dynamic simulations were performed to elucidate the molecular determinant of the enzyme activity. Our simulations show that the substrate binds much more strongly in the A147I/V148F/G254A mutant than in wild type, with more hydrogen bonds formed between the substrate and the catalytic triad and the oxyanion hole.

Unveiling the Atomic-Level Determinants of Acylase–Ligand Complexes: An Experimental and Computational Study

Luca Mollica, Gianluca Conti, Loredano Pollegioni, Andrea Cavalli, and Elena Rosini [Università degli studi dell’Insubria]

J.Chem. Infor. and Mod. **55**, 2227–2241, 2015.

We recently enhanced the catalytic efficiency on CephC of a glutaryl acylase from *Pseudomonas* N176 (named VAC) by a protein engineering approach and solved the crystal structures of wild-type VAC and the H57βS–H70βS VAC double variant. In the present work, experimental measurements on several CephC derivatives and six VAC variants were carried out, and the binding of ligands into the VAC active site was investigated at an atomistic level by means of molecular docking and molecular dynamics simulations and analyzed on the basis of the molecular geometry of encounter complex formation and protein–ligand potential of mean force profiles.

Activity prediction of substrates in NADH-dependent carbonyl reductase by docking requires catalytic constraints and charge parameterization of catalytic zinc environment

Gaurao V. Dhoke, Christoph Loderer, Mehdi D. Davari, Marion Ansorge-Schumacher, Ulrich Schwaneberg, Marco Bocola [RWTH Aachen University]

J.Comp.Aided. Mol.des. **29**, 1057-1069, 2015.

Molecular docking of substrates is more challenging compared to inhibitors as the reaction mechanism has to be considered. This becomes more pronounced for zinc-dependent enzymes since the coordination state of the catalytic zinc ion is of greater importance. In order to develop a predictive substrate docking protocol, we have performed molecular docking studies of diketone substrates using the catalytic state of carbonyl reductase 2. We selected the catalytic binding pose of each substrate by applying mechanism based distance criteria.

Protein-Protein Interactions

In silico and experimental validation of protein–protein interactions between PknI and Rv2159c from *Mycobacterium tuberculosis*

Arunkumar Venkatesan, Sameer Hassan, Kannan Palaniyandi, Sujatha Narayanan [National Institute for Research in Tuberculosis, Chennai]

J. Mol.Graph. and Mod., **62**, 283-293, 2015.

Protein–protein interactions control the diverse and essential molecular processes inside the cell. To maintain the cellular physiology, protein kinases not only signal their substrates through reversible phosphorylation, but they also physically interact with them. PknI, a serine/threonine protein kinase of *Mycobacterium tuberculosis* is known to be important for cellular homeostasis. In this study, we have identified the interacting proteins for PknI. We screened for proteins interacting with PknI using an in vitro assay, Far-western blot. This protein kinase specifically interacts with two peroxidase proteins of *M. tuberculosis*, Rv2159c and Rv0148. The PknI–Rv2159c interaction pair was further studied for the critical amino acid residues in Rv2159c that are responsible for the interaction.

Knowledge of Native Protein–Protein Interfaces Is Sufficient To Construct Predictive Models for the Selection of Binding Candidates

Petr Popov and Sergei Grudinin [Université Grenoble Alpes]

J.Chem. Infor. and Mod. **55**, 2242–2255, 2015.

Selection of putative binding poses is a challenging part of virtual screening for protein–protein interactions. Predictive models to filter out binding candidates with the highest binding affinities comprise scoring functions that assign a score to each binding pose. Existing scoring functions are typically deduced by collecting statistical information about interfaces of native conformations of protein complexes along with interfaces of a large generated set of non-native conformations. The present study demonstrates that knowledge of only native protein–protein interfaces is sufficient to construct well-discriminative predictive models for the selection of binding candidates.

Membrane Proteins and Lipid Peptide Interactions

α -Tocopherol Is Well Designed to Protect Polyunsaturated Phospholipids: MD Simulations

Xiaoling Leng, Jacob J. Kinnun, Drew Marquardt, Mikel Ghefli, Norbert Kučerka, John Katsaras, Jeffrey Atkinson, Thad A. Harroun, Scott E. Feller, Stephen R. Wassall [Indiana University-Purdue University Indianapolis]

Biophysical Journal. **109**, 1608-1618, 2015.

The presumptive function for alpha-tocopherol (α toc) in membranes is to protect polyunsaturated lipids against oxidation. Although the chemistry of the process is well established, the role played by molecular structure that we address here with atomistic molecular-dynamics simulations remains controversial. The simulations were run in the constant particle NPT ensemble on hydrated lipid bilayers composed of SDPC (1-stearoyl-2-docosaheptaenoylphosphatidylcholine, 18:0-22:6PC) and SOPC (1-stearoyl-2-oleoylphosphatidylcholine, 18:0-18:1PC) in the presence of 20 mol % α toc at 37°C.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Effect of the N-Terminal Helix and Nucleotide Loading on the Membrane and Effector Binding of Arl2/3

Shobhna Kapoor, Eyad K. Fansa, Simone Möbitz, Shehab A. Ismail, Roland Winter, Alfred Wittinghofer, Katrin Weise [TU Dortmund University, Dortmund]

Biophysical Journal. **109**, 1619-1629, 2015.

The small GTP-binding proteins Arl2 and Arl3, which are close homologs, share a number of interacting partners and act as displacement factors for prenylated and myristoylated cargo. Nevertheless, both proteins have distinct biological functions. Whereas Arl3 is considered a ciliary protein, Arl2 has been reported to be involved in tubulin folding, mitochondrial function, and Ras signaling. How these different roles are attained by the two homolog proteins is not fully understood. Recently, we showed that the N-terminal amphipathic helix of Arl3, but not that of Arl2, regulates the release of myristoylated ciliary proteins from the GDI-like solubilizing factor UNC119a/b.

Can Specific Protein-Lipid Interactions Stabilize an Active State of the Beta 2 Adrenergic Receptor?

Chris Neale, Henry D. Herce, Régis Pomès, Angel E. García [Rensselaer Polytechnic Institute]

Biophysical Journal. **109**, 1652-1662, 2015.

G-protein-coupled receptors are eukaryotic membrane proteins with broad biological and pharmacological relevance. Like all membrane-embedded proteins, their location and orientation are influenced by lipids, which can also impact protein function via specific interactions. Extensive simulations totaling 0.25 ms reveal a process in which phospholipids from the membrane's cytosolic leaflet enter the empty G-protein binding site of an activated β_2 adrenergic receptor and form salt-bridge interactions that inhibit ionic lock formation and prolong active-state residency.

Arginine-, d-arginine-vasopressin, and their inverso analogues in micellar and liposomic models of cell membrane: CD, NMR, and molecular dynamics studies

Emilia A. Lubecka [University of Gdańsk], Emilia Sikorska, Dariusz Sobolewski, Adam Prah, Jiřina Slaninová, Jerzy Ciarkowski

Eur.Biophy., **44**, 727-743, 2015.

We describe the synthesis, pharmacological properties, and structures of antidiuretic agonists, arginine vasopressin (AVP) and [d-Arg⁸]-vasopressin (DAVP), and their inverso analogues. The structures of the peptides are studied based on micellar and liposomic models of cell membranes using CD spectroscopy. Additionally, three-dimensional structures in mixed anionic-zwitterionic micelles are obtained using NMR spectroscopy and molecular dynamics simulations. NMR data have shown that AVP and DAVP tend to adopt typical of vasopressin-like peptides β -turns: in the 2–5 and 3–6 fragments.

Assessment and acceleration of binding energy calculations for protein-ligand complexes by the fragment molecular orbital method

Takao Otsuka, Noriaki Okimoto [RIKEN Quantitative Biology Center] and Makoto Taiji

J. Comp. Chem., **36**, 2209–2218, 2015.

In the field of drug discovery, it is important to accurately predict the binding affinities between target proteins and drug applicant molecules. Many of the computational methods available for evaluating binding affinities have adopted molecular mechanics-based force fields, although they cannot fully describe protein-ligand interactions. A noteworthy computational method in development involves large-scale electronic structure calculations. Fragment molecular orbital (FMO) method, which is one of such large-scale calculation techniques, is applied in this study for calculating the binding energies between proteins and ligands.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Accounting for Intraligand Interactions in Flexible Ligand Docking with a PMF-Based Scoring Function

A. Y. Lizunov [Moscow Institute of Physics and Technology], A. L. Gonchar, N. I. Zaitseva, and V. V. Zosimov

J.Chem. Infor. and Mod. **55**, 2121–2137, 2015.

We analyzed the frequency with which intraligand contacts occurred in a set of 1300 protein–ligand complexes [Plewczynski et al. *J. Comput. Chem.* 2011, 32, 742–755.]. Our analysis showed that flexible ligands often form intraligand hydrophobic contacts, while intraligand hydrogen bonds are rare. The test set was also thoroughly investigated and classified. We suggest a universal method for enhancement of a scoring function based on a potential of mean force (PMF-based score) by adding a term accounting for intraligand interactions.

Applications of MMPBSA to Membrane Proteins I: Efficient Numerical Solutions of Periodic Poisson–Boltzmann Equation

Wesley M. Botello-Smith and Ray Luo [University of California, Irvine]

J.Chem. Infor. and Mod. **55**, 2187–2199, 2015.

Continuum solvent models have been widely used in biomolecular modeling applications. Recently much attention has been given to inclusion of implicit membranes into existing continuum Poisson–Boltzmann solvent models to extend their applications to membrane systems. Inclusion of an implicit membrane complicates numerical solutions of the underlining Poisson–Boltzmann equation due to the dielectric inhomogeneity on the boundary surfaces of a computation grid. This can be alleviated by the use of the periodic boundary condition, a common practice in electrostatic computations in particle simulations.

The Effect of Membrane Environment on Surfactant Protein C Stability Studied by Constant-pH Molecular Dynamics

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

J.Chem. Infor. and Mod. **55**, 2206–2217, 2015.

Pulmonary surfactant protein C (SP-C) is a small peptide with two covalently linked fatty acyl chains that plays a crucial role in the formation and stabilization of the pulmonary surfactant reservoirs during the compression and expansion steps of the respiratory cycle. Although its function is known to be tightly related to its highly hydrophobic character and key interactions maintained with specific lipid components, much is left to understand about its molecular mechanism of action. In this work, the conformational behavior of both the acylated and deacylated SP-C isoforms was studied in a DPPC bilayer under different pH conditions using constant-pH molecular dynamics simulations.

WONKA: objective novel complex analysis for ensembles of protein–ligand structures

A. R. Bradley, I. D. Wall, F. von Delft, D. V. S. Green, C. M. Deane, B. D. Marsden [Nuffield Department of Medicine, University of Oxford]

J.Comp.Aided. Mol.des. **29**, 963–973, 2015.

WONKA is a tool for the systematic analysis of an ensemble of protein–ligand structures. It makes the identification of conserved and unusual features within such an ensemble straightforward. WONKA uses an intuitive workflow to process structural co-ordinates. Ligand and protein features are summarised and then presented within an interactive web application. WONKA's power in consolidating and summarising large amounts of data is described through the analysis of three bromodomain datasets.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Combination of MD Simulations with Two-State Kinetic Rate Modeling Elucidates the Chain Melting Transition of Phospholipid Bilayers for Different Hydration Levels

Bartosz Kowalik, Thomas Schubert, Hirofumi Wada, Motomu Tanaka, Roland R. Netz, and Emanuel Schneck [Max Planck Institute of Colloids and Interfaces]

J. Phys. Chem. B., **119**, 14157–14167, 2015.

The phase behavior of membrane lipids plays an important role in the formation of functional domains in biological membranes and crucially affects molecular transport through lipid layers, for instance, in the skin. We investigate the thermotropic chain melting transition from the ordered L_β phase to the disordered L_α phase in membranes composed of dipalmitoylphosphatidylcholine (DPPC) by atomistic molecular dynamics simulations in which the membranes are subject to variable heating rates. We find that the transition is initiated by a localized nucleus and followed by the propagation of the phase boundary.

Atomistic Molecular Simulations Suggest a Kinetic Model for Membrane Translocation by Arginine-Rich Peptides

Delin Sun, Jan Forsman, and Clifford E. Woodward [University of New South Wales]

J. Phys. Chem. B., **119**, 14413–14420, 2015.

Arginine-rich cell penetrating peptides (ARCPPs) are known to quickly permeate cell membranes through a non-endocytotic pathway. Potential clinical applications of this facility have prompted enormous effort, both experimental and theoretical, to better understand how ARCPPs manage to overcome the prodigious thermodynamic cost of lipid bilayer permeation by these highly charged peptides. In this work we report the results of all-atom simulations, which suggest that a kinetic (rather than thermodynamic) mechanism may explain how ARCPPs are able to achieve this.

Simulating Gram-Negative Bacterial Outer Membrane: A Coarse Grain Model

Huilin Ma, Flaviyan Jerome Irudayanathan, Wenjuan Jiang, and Shikha Nangia [Syracuse University, Syracuse]

J. Phys. Chem. B., **119**, 14668–14682, 2015.

The cell envelope of Gram-negative bacteria contains a lipopolysaccharide (LPS) rich outer membrane that acts as the first line of defense for bacterial cells in adverse physical and chemical environments. The LPS macromolecule has a negatively charged oligosaccharide domain that acts as an ionic brush, limiting the permeability of charged chemical agents through the membrane. We have developed a coarse grained force field for outer membrane that is computationally affordable for simulating dynamical process over physiologically relevant time scales.

Extension of a protein docking algorithm to membranes and applications to amyloid precursor protein dimerization

Shruthi Viswanath, Laura Dominguez, Leigh S. Foster, John E. Straub and Ron Elbe [University of Texas at Austin]

Proteins: Stru. Fun. & Bioinf., **83**, 2170–2185, 2015.

Novel adjustments are introduced to the docking algorithm, DOCK/PIERR, for the purpose of predicting structures of transmembrane protein complexes. Incorporating knowledge about the membrane environment is shown to significantly improve docking accuracy. The extended version of DOCK/PIERR is shown to perform comparably to other leading docking packages. This membrane version of DOCK/PIERR is applied to the prediction of coiled-coil homodimer structures of the transmembrane region of the C-terminal peptide of amyloid precursor protein (C99). Results from MD simulation of the C99 homodimer in POPC bilayer and docking are compared.

Protein-Nucleic acid Interactions

DNA Backbone BI/BII Distribution and Dynamics in E2 Protein-Bound Environment Determined by Molecular Dynamics Simulations

James C. Robertson and Thomas E Cheatham, III [The University of Utah, Salt Lake City]

J. Phys. Chem. B., **119**, 14111–14119, 2015.

BI and BII conformational substates in the DNA backbone typify canonical B-form DNA. The BI and BII substates are important for structural variation of DNA and have been implicated in protein–nucleic acid recognition mechanisms. Recent refinements have been made to nucleic acid force fields employed in molecular dynamics simulations that demonstrate a better ability to model the BI and BII states, leading to overall improved modeling of DNA structure and dynamics. These force field improvements have yet to be significantly demonstrated in the context of a protein–DNA system extended to long time scales.

Protein–Drug Interactions with Effective Polarization in Polarizable Water: Oxime Unbinding from AChE Gorge

Arup K. Pathak and Tusar Bandyopadhyay [Bhabha Atomic Research Centre]

J. Phys. Chem. B., **119**, 14460–14471, 2015.

Despite the fact that polarizability of water is different in the bulk and in protein, simulations of protein–ligand complexes are mostly carried out in nonpolarizable water media. We present oxime (HI-6) unbinding from the active site gorge of AChE, known to be strongly influenced by intermolecular cation- π , hydrogen bridge (HB) and water bridge (WB) interactions and by molecular simulations with effective polarization in polarizable mean-field model of TIP3P water. Enabled by the recent availability of a method of obtaining microkinetics of rare events, we set out to investigate the rate constants of unbinding transitions from one basin to the other through a combination of metadynamics and hyperdynamics simulations.

R248Q mutation—Beyond p53-DNA binding

Jeremy W. K. Ng, Dilraj Lama, Suryani Lukman, David P. Lane, Chandra S. Verma and Adelene Y. L. Sim [Agency for Science, Technology, and Research, 30 Biopolis Street]

Proteins: Stru. Fun. & Bioinf., **83**, 2240–2250, 2015.

R248 in the DNA binding domain (DBD) of p53 interacts directly with the minor groove of DNA. Earlier nuclear magnetic resonance (NMR) studies indicated that the R248Q mutation resulted in conformation changes in parts of DBD far from the mutation site. However, how information propagates from the mutation site to the rest of the DBD is still not well understood. We performed a series of all-atom molecular dynamics (MD) simulations to dissect sterics and charge effects of R248 on p53-DBD conformation: (i) wild-type p53 DBD; (ii) p53 DBD with an electrically neutral arginine side-chain; (iii) p53 DBD with R248A; (iv) p53 DBD with R248W; and (v) p53 DBD with R248Q.

Nucleic Acids

Enhancing DNA-Mediated Assemblies of Supramolecular Cage Dimers through Tuning Core Flexibility and DNA Length—A Combined Experimental–Modeling Study

Bong Jin Hong, Vincent Y. Cho, Reiner Bleher, George C. Schatz, and SonBinh T. Nguyen [Northwestern University, Evanston]

J. Am. Chem. Soc., **137**, 13381–13388, 2015.

Two complementary small-molecule–DNA hybrid (SMDH) building blocks have been combined to form well-defined supramolecular cage dimers at DNA concentrations as high as 102 μ M. This was made possible by combining a flexible small-molecule core and three DNA arms of moderate lengths (<20 base pairs). These results were successfully modeled by coarse-grained molecular dynamics simulations, which also revealed that the formation of ill-defined networks in the case of longer DNA arms can be significantly biased by the presence of deep kinetic traps.

Integrating DNA-Strand-Displacement Circuitry with Self-Assembly of Spherical Nucleic Acids

Dongbao Yao, Tingjie Song, Xianbao Sun, Shiyan Xiao, Fujian Huang, and Haojun Liang [University of Science and Technology of China]

J. Am. Chem. Soc., **137**, 14107–14113, 2015.

Programmable and algorithmic behaviors of DNA molecules allow one to control the structures of DNA-assembled materials with nanometer precision and to construct complex networks with digital and analog behaviors. Here we developed a way of integrating a DNA-strand-displacement circuit with self-assembly of spherical nucleic acids, wherein a single DNA strand was used to initiate and catalyze the operation of upstream circuits to release a single strand that subsequently triggers self-assembly of spherical nucleic acids in downstream circuits, realizing a programmable kinetic control of self-assembly of spherical nucleic acids.

DNA Structural Correlation in Short and Long Ranges

Chan Gu, Jun Zhang, Y. Isaac Yang, Xi Chen, Hao Ge, Yujie Sun, Xiaodong Su, Lijiang Yang, Sunney Xie, and Yi Qin Gao [Peking University]

J. Phys. Chem. B., **119**, 13980–13990, 2015.

Recent single-molecule measurements have revealed the DNA allostery in protein/DNA binding. MD simulations showed that this allosteric effect is associated with the deformation properties of DNA. In this study, we used MD simulations to further investigate the mechanism of DNA structural correlation, its dependence on DNA sequence, and the chemical modification of the bases. Besides a random sequence, poly d(AT) and poly d(GC) are also used as simpler model systems, which show the different bending and twisting flexibilities.

pKa predictions for proteins, RNAs, and DNAs with the Gaussian dielectric function using DelPhi pKa

Lin Wang, Lin Li and Emil Alexov [Clemson University, Clemson]

Proteins: Stru. Fun. & Bioinf., **83**, 2186–2197, 2015.

We developed a Poisson-Boltzmann based approach to calculate the pK_a values of protein ionizable residues (Glu, Asp, His, Lys and Arg), nucleotides of RNA and single stranded DNA. Two novel features were utilized: the dielectric properties of the macromolecules and water phase were modeled via the smooth Gaussian-based dielectric function in DelPhi and the corresponding electrostatic energies were calculated without defining the molecular surface. We tested the algorithm by calculating pK_a values for more than 300 residues from 32 proteins from the PPD dataset and achieved an overall RMSD of 0.77.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Development of quantitative structure activity relationships for the binding affinity of methoxypyridinium cations for human acetylcholinesterase

Jason A. Morrill [University of Iowa], Joseph J. Topczewski, Alexander M. Lodge, Nilanthi Yasapala, Daniel M. Quinn

J. Mol. Graph. and Mod., **62**, 181-18 , 2015.

Among the most toxic substances known are the organophosphorus (OP) compounds used as pesticides and chemical warfare agents. Owing to their high toxicity there is a number of efforts underway to develop effective therapies for OP agent exposure. To date all therapies in use treat inhibited acetylcholinesterase (AChE), but are ineffective for the treatment of inhibited AChE, which has undergone a subsequent hydrolysis process, referred to as aging. Toward developing a therapy for treating victims of OP intoxication in the aged state we have developed Quantitative Structure-Activity Relationships (QSARs) based on the AM1 semiempirical quantum mechanical method using the program, CODESSA (COMprehensive Descriptors for Structural and Statistical Analysis).

Harmonization of QSAR Best Practices and Molecular Docking Provides an Efficient Virtual Screening Tool for Discovering New G-Quadruplex Ligands

Daimel Castillo-González, Jean-Louis Mergny, Aurore De Rache, Gisselle Pérez-Machado, Miguel Angel Cabrera-Pérez, Orazio Nicolotti, Antonellina Introcaso, Giuseppe Felice Mangiatordi, Aurore Guédin, Anne Bourdoncle, Teresa Garrigues, Federico Pallardó, M. Natália D. S. Cordeiro, Cesar Paz-y-Miño, Eduardo Tejera, Fernanda Borges [Universidade do Porto], and Maykel Cruz-Monteagudo

J. Chem. Infor. and Mod. **55**, 2094–2110, 2015.

Telomeres and telomerase are key players in tumorigenesis. Among the various strategies proposed for telomerase inhibition or telomere uncapping, the stabilization of telomeric G-quadruplex (G4) structures is a very promising one. Additionally, G4 stabilizing ligands also act over tumors mediated by the alternative elongation of telomeres. We applied a virtual screening strategy based on the rigorous application of QSAR best practices and its harmonized integration with structure-based methods. More than 600,000 compounds from commercial databases were screened, the first 99 compounds were prioritized, and 21 commercially available and structurally diverse candidates were purchased and submitted to experimental assays.

Potentials and Parameters

A consistent S-Adenosylmethionine force field improved by dynamic Hirshfeld-I atomic charges for biomolecular simulation

David Adrian Saez, Esteban Vöhringer-Martinez [Universidad de Concepción]

J. Comp. Aided. Mol. des. **29**, 951-961, 2015.

S-Adenosylmethionine (AdoMet) is involved in many biological processes as cofactor in enzymes transferring its sulfonium methyl group to various substrates. Additionally, it is used as drug and nutritional supplement to reduce the pain in osteoarthritis and against depression. Due to the biological relevance of AdoMet it has been part of various computational simulation studies and will also be in the future. Here, we use electronic structure calculations combined with molecular dynamics simulations in explicit solvent to develop force field parameters compatible with the AMBER99 force field.

Molecular Dynamics

Increased Energy Demand during Adrenergic Receptor Stimulation Contributes to Ca^{2+} Wave Generation

Elisa Bovo, Stefan R. Mazurek, Pieter P. de Tombe, Aleksey V. Zima [Stritch School of Medicine]

Biophysical Journal. **109**, 1583-1591, 2015.

While β -adrenergic receptor (β -AR) stimulation ensures adequate cardiac output during stress, it can also trigger life-threatening cardiac arrhythmias. We have previously shown that proarrhythmic Ca^{2+} waves during β -AR stimulation temporally coincide with augmentation of reactive oxygen species (ROS) production. In this study, we tested the hypothesis that increased energy demand during β -AR stimulation plays an important role in mitochondrial ROS production and Ca^{2+} -wave generation in rabbit ventricular myocytes. We found that β -AR stimulation with isoproterenol (0.1 μM) decreased the mitochondrial redox potential and the ratio of reduced to oxidized glutathione.

Molecular simulation assisted identification of Ca^{2+} binding residues in TMEM16A

Chun-Li Pang, Hong-Bo Yuan, Tian-Guang Cao, Ji-Guo Su, Ya-Fei Chen, Hui Liu, Hui Yu, Hai-Ling Zhang, Yong Zhan, Hai-Long An [Key laboratory of Molecular Biophysics, Tianjin], Yue-Bin Han

J.Comp.Aided. Mol.des. **29**, 1035-1043, 2015.

Calcium-activated chloride channels (CaCCs) play vital roles in a variety of physiological processes. Transmembrane protein 16A (TMEM16A) has been confirmed as the molecular counterpart of CaCCs which greatly pushes the molecular insights of CaCCs forward. However, the detailed mechanism of Ca^{2+} binding and activating the channel is still obscure. Here, we utilized a combination of computational and electrophysiological approaches to discern the molecular mechanism by which Ca^{2+} regulates the gating of TMEM16A channels. The simulation results show that the first intracellular loop serves as a Ca^{2+} binding site including D439, E444 and E447.

QM and QM/MM

Transannular [6 + 4] and Ambimodal Cycloaddition in the Biosynthesis of Heronamide A

Peiyuan Yu, Ashay Patel, and K. N. Houk [University of California, Los Angeles]

J. Am. Chem. Soc., **137**, 13518–13523, 2015.

The transannular [6 + 4] cycloaddition proposed as a step in the biosynthesis of heronamide A has been modeled using density functional theory. The proposed cycloaddition is highly stereoselective, affording a single product. The reaction proceeds through an ambimodal transition state that directly leads to a [4 + 2] adduct in addition to the observed [6 + 4] adduct. Interconversion of these adducts is possible via a facile Cope rearrangement. The [6 + 4] adduct is thermodynamically more stable than the [4 + 2] adduct by 5.2 kcal mol⁻¹ due to a combination of the ring and steric strain in the [4 + 2] product.

QM and QM/MM (Cont'd)

Cooperativity in bimetallic glutathione complexes

Sadhana Kumbhar, Saibal Jana, Anakuthil Anoop, Mark P. Waller [Westfälische Wilhelms Universität Münster]

J. Mol. Graph. and Mod., **62**, 1-10, 2015.

Glutathione interacting with Au^+ , Ag^+ , and $[\text{HgMe}]^+$ metal ions is investigated using density functional theory. An extensive conformational search shows that the sulfhydryl group of cysteine is the predominant binding motif for Au^+ , Ag^+ , and $[\text{HgMe}]^+$. The order of binding affinities and binding free energies for the metal:ligand complexes are calculated at the B3LYP-D3(BJ)/def2-TZVP level of theory. Analysis of the gas-phase optimized structures has shown that the increase in the number of metal ions ($1:1 \rightarrow 2:1$) during the complex formation with a single glutathione leads to a strong cooperative behavior.

Role of Water in the Puzzling Mechanism of the Final Aromatization Step Promoted by the Human Aromatase Enzyme. Insights from QM/MM MD Simulations

Jacopo Sgrignani, Marcella Iannuzzi, and Alessandra Magistrato [CNR-IOM-Democritos National Simulation Center]

J. Chem. Infor. and Mod. **55**, 2218–2226, 2015.

The enzyme human aromatase (HA) catalyzes the conversion of androgens to estrogens via two hydroxylation reactions and a final unique aromatization step. Despite the great interest of HA as a drug target against breast cancer detailed structural and spectroscopic information on this enzyme became available only in the past few years. As such, the enigmatic mechanism of the final aromatization step is still a matter of debate. Here, we investigated the final step of the HA enzymatic cycle via hybrid quantum-classical (QM/MM) metadynamics and blue-moon ensemble simulations.

Comparative or Homology Modeling

Application of learning to rank to protein remote homology detection

Bin Liu [Harbin Institute of Technology Shenzhen Graduate School], Junjie Chen, and Xiaolong Wang

Bioinformatics, **31**, 3492-3498, 2015.

Protein remote homology detection is one of the fundamental problems in computational biology, aiming to find protein sequences in a database of known structures that are evolutionarily related to a given query protein. Some computational methods treat this problem as a ranking problem and achieve the state-of-the-art performance, such as PSI-BLAST, HHblits and ProtEmbed. Experimental results on a widely used benchmark dataset showed that ProtDec-LTR can achieve an ROC1 score of 0.8442 and an ROC50 score of 0.9023 outperforming all the individual predictors and some state-of-the-art methods.

Ligand Docking

High-order neural networks and kernel methods for peptide-MHC binding prediction

Pavel P. Kuksa, Martin Renqiang Min, Rishabh Dugar, and Mark Gerstein [Yale University, New Haven]

Bioinformatics, **31**, 3600-3607, 2015.

Effective computational methods for peptide-protein binding prediction can greatly help clinical peptide vaccine search and design. However, previous computational methods fail to capture key nonlinear high-order dependencies between different amino acid positions. As a result, they often produce low-quality rankings of strong binding peptides. The proposed high-order methods improve quality of binding predictions over other prediction methods. With the proposed methods, a significant gain of up to 25–40% is observed on the benchmark and reference peptide datasets and tasks. In addition, for the first time, our experiments show that pre-training with high-order semi-restricted Boltzmann machines significantly improves the performance of feed-forward HONNs.

Thiol versus hydroxamate as zinc binding group in HDAC inhibition: An Ab initio QM/MM molecular dynamics study

Wenjing Gong, Ruibo Wu and Yingkai Zhang [New York University, New York]

J. Comp. Chem., **36**, 2228–2235, 2015.

Zinc-dependent histone deacetylases (HDACs) play a critical role in transcriptional repression and gene silencing, and are among the most attractive targets for the development of new therapeutics against cancer and various other diseases. Two HDAC inhibitors have been approved by FDA as anti-cancer drugs: one is SAHA whose hydroxamate is directly bound to zinc, the other is FK228 whose active form may use thiol as the zinc binding group. In this work, our computational approaches center on Born–Oppenheimer ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics with umbrella sampling, which allow for modeling of the zinc active site with reasonable accuracy while properly including dynamics and effects of protein environment.

Entropy in bimolecular simulations: A comprehensive review of atomic fluctuations-based methods

Summer Kassem, Marawan Ahmed, Salah El-Sheikh, Khaled H. Barakat [University of Alberta]

J. Mol.Graph. and Mod., **62**, 105-117, 2015.

Entropy of binding constitutes a major, and in many cases a detrimental, component of the binding affinity in biomolecular interactions. While the enthalpic part of the binding free energy is easier to calculate, estimating the entropy of binding is further more complicated. A precise evaluation of entropy requires a comprehensive exploration of the complete phase space of the interacting entities. Most of these golden standard methods focused on developing a reliable estimation of the conformational part of the entropy. Here, we review these methods with a particular emphasis on the different techniques that extract entropy from atomic fluctuations.

Ligand Docking (Cont'd)

A structural insight into the inhibitory mechanism of an orally active PI3K/mTOR dual inhibitor, PKI-179 using computational approaches

Mohd Rehan [King Abdulaziz University]

J. Mol.Graph. and Mod., **62**, 226-234, 2015.

The PI3K/AKT/mTOR signaling pathway has been identified as an important target for cancer therapy. Attempts are increasingly made to design the inhibitors against the key proteins of this pathway for anti-cancer therapy. The PI3K/mTOR dual inhibitors have proved more effective than the inhibitors against only single protein targets. Recently discovered PKI-179, an orally effective compound, is one such dual inhibitor targeting both PI3K and mTOR. This anti-cancer compound is efficacious both in vitro and in vivo. The current study investigated the exact binding mode and the molecular interactions of PKI-179 with PI3K γ and mTOR using molecular docking and (un)binding simulation analyses.

PKR-inhibitor binds efficiently with human microtubule affinity-regulating kinase 4

Farha Naz, Mohd. Shahbaaz, Shama Khan, Krishna Bisetty, Asimul Islam, Faizan Ahmad, Md. Imtaiyaz Hassan [Jamia Millia Islamia, Jamia Nagar]

J. Mol.Graph. and Mod., **62**, 245-252 , 2015.

MAP/microtubule affinity-regulating kinase 4 (MARK4) plays a central role in the cellular physiology, and it is inseparably linked with many human diseases including cancer, diet induced obesity, type2 diabetes and neurodegenerative disorders. Here, we studied the interaction of PKR-inhibitor with two variants of human MARK4. One variant is named as MARK4-F1 which has 59 N-terminal residues along with kinase domain while another variant is MARK4-F2 which has kinase domain only. Molecular-docking, molecular dynamics (MD) simulation and fluorescence-binding studies were undertaken to understand the role of N-terminal 59-residues in the binding of substrate/inhibitors.

A Pipeline To Enhance Ligand Virtual Screening: Integrating Molecular Dynamics and Fingerprints for Ligand and Proteins

Francesca Spyarakis, Paolo Benedetti, Sergio Decherchi, Walter Rocchia, Andrea Cavalli, Stefano Alcaro, Francesco Ortuso, Massimo Baroni, and Gabriele Cruciani [University of Perugia]

J.Chem. Infor. and Mod. **55**, 2256–2274, 2015.

The importance of taking into account protein flexibility in drug design and virtual ligand screening (VS) has been widely debated in the literature, and molecular dynamics (MD) has been recognized as one of the most powerful tools for investigating intrinsic protein dynamics. Nevertheless, deciphering the amount of information hidden in MD simulations and recognizing a significant minimal set of states to be used in virtual screening experiments can be quite complicated. Here we present an integrated MD–FLAP (molecular dynamics–fingerprints for ligand and proteins) approach, comprising a pipeline of molecular dynamics, clustering and linear discriminant analysis, for enhancing accuracy and efficacy in VS campaigns.

Ligand Docking (Cont'd)

Ultrafast protein structure-based virtual screening with Panther

Sanna P. Niinivehmas, Kari Salokas, Sakari Lätti, Hannu Raunio, Olli T. Pentikäinen [University of Jyväskylä]

J.Comp.Aided. Mol.des. **29**, 989-1006, 2015.

Molecular docking is by far the most common method used in protein structure-based virtual screening. This paper presents Panther, a novel ultrafast multipurpose docking tool. In Panther, a simple shape-electrostatic model of the ligand-binding area of the protein is created by utilizing the protein crystal structure. The features of the possible ligands are then compared to the model by using a similarity search algorithm. On average, one ligand can be processed in a few minutes by using classical docking methods, whereas using Panther processing takes <1 s.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 62, November, 2015.

- 1-10 **Cooperativity in bimetallic glutathione complexes**, Sadhana Kumbhar, Saibal Jana, Anakuthil Anoop, Mark P. Waller [Westfälische Wilhelms Universität Münster]

See Methodology / QM and QM/MM.

- 11-17 **Inclusion complex thermodynamics: The β -cyclodextrin and sertraline complex example**, Juliana Fedoce Lopes, Clebio S. Nascimento Jr., Cleber P.A. Anconi, H lio F.Dos Santos, Wagner B.De Almeida [Universidade Federal Fluminense]

Thermodynamic properties for β -cyclodextrin-Sertraline inclusion process was calculated at the density functional theory (DFT) level using the PBE0 functional with 6-31G(d,p), 6-31++G(d,p) and 6-311++G(2df,p) basis sets.

- 18-25 **Sterols and triterpenoids as potential anti-inflammatories: Molecular docking studies for binding to some enzymes involved in inflammatory pathways**, Marco A. Loza-Mej a, Juan Rodrigo Salazar [Universidad La Salle]

See Applications / Medicinal Chemistry and Drug Design.

- 26-37 **On novel magnetic probe for fullerene characterization: Theoretical studies on NMR parameters of free and confined in fullerenes HD and H₂ molecules**, Marzena Jankowska, Teobald Kupka [University of Opole], Leszek Stobi nsk

Chemical characterization and separation of individual fullerenes from a raw reaction mixture need new and efficient tools, including rapid spectroscopic techniques. In this work we report on quantum-chemical prediction of nuclear magnetic shielding (and chemical shift) and indirect spin-spin coupling constant in free HD and H₂ molecules, as well as models of confined dihydrogen using the coupled cluster with single and double excitations (CCSD) and density functional theory (DFT) levels of theory.

- 38-42 **Molecular dynamics simulation of temperature profile in partially hydrogenated graphene and graphene with grain boundary**, Erfan Lotfi, M. Neek-Amal [Islamic Azad University], M. Elahi

Temperature profile in graphene, graphene with grain boundary and vacancy defects and hydrogenated graphene with different percentage of H-atoms are determined using molecular dynamics simulation.

- 43-55 **Comparison of templates for homology model of $\rho 1$ GABA_c receptors: More insights to the orthosteric binding site's structure and functionality**, Moawiah M Naffaa, Mary Chebib, David E Hibbs, Jane R Hanrahan [University of Sydney]

See Applications / Homology Modeling.

- 56-68 **Anti-tubercular drug development: computational strategies to identify potential compounds**, Sanchaita Rajkhowa, Anupam Nath Jha, Ramesh Chandra Deka [Tezpur University, Napaam]

See Applications / Medicinal Chemistry and Drug Design.

- 69-73 **Coarse-grained molecular dynamics simulation of water diffusion in the presence of carbon nanotubes**, Isabel Lado Touriño, Arisbel Cerpa Naranjo, Viviana Negri, Sebastián Cerdán, Paloma Ballesteros [Faculty of Sciences, UNED]

See Applications / Carbon Nanotubes.

- 74-80 **Thermal conductivity and heat transport properties of nitrogen-doped graphene**, Elaheh K. Goharshadi [Ferdowsi University of Mashhad], Sayyed Jalil Mahdizadeh

In the present study, the thermal conductivity (TC) and heat transport properties of nitrogen doped graphene (N-graphene) were investigated as a function of temperature (107–400 K) and N-doped concentration (0.0–7.0%) using equilibrium molecular dynamics simulation based on Green–Kubo method.

- 81-86 **Impact sensitivities of energetic materials: Exploring the limitations of a model based only on structural formulas**, Didier Mathieu [CEA, DAM, Le Ripault], Thibaud Alaime

Using a comprehensive set of drop weight impact test data (h_{50}) newly compiled from literature for 308 materials, a recent approach to predict impact sensitivities of nitro compounds is generalized to most explosive substances of interest.

- 87-96 **Conformational variation of an extreme drug resistant mutant of HIV protease**, Chen-Hsiang Shen, Yu-Chung Chang, Johnson Agniswamy, Robert W. Harrison, Irene T. Weber [Georgia State University]

See Applications / Medicinal Chemistry and Drug Design.

- 97-104 **Identification and characterization of a glycosaminoglycan binding site on interleukin-10 via molecular simulation methods**, Jan-Philip Gehrcke, M. Teresa Pisabarro [Structural Bioinformatics, BIOTEC]

See Applications / Ligand Binding.

- 105-117 **Entropy in bimolecular simulations: A comprehensive review of atomic fluctuations-based methods**, Summer Kassem, Marawan Ahmed, Salah El-Sheikh, Khaled H. Barakat [University of Alberta]

See Methodology / Ligand Docking.

- 118-127 **PrinCCes: Continuity-based geometric decomposition and systematic visualization of the void repertoire of proteins**, Gábor Cziráj [Semmelweis University]

See Applications / Protein Dynamics.

- 128-137 **Toxicity prediction of PHDDs and phenols in the light of nucleic acid bases and DNA base pair interaction**, Sutapa Mondal Roy [S. V. National Institute of Technology], Debesh R. Roy, Suban K. Sahoo

The applicability of Density Functional Theory (DFT) based descriptors for the development of quantitative structure-toxicity relationships (QSTR) is assessed for two different series of toxic aromatic compounds, viz., polyhalogenated dibenzo-p-dioxins (PHDDs) and phenols (PHs).

- 138-149 **Elucidation of the binding mechanism of renin using a wide array of computational techniques and biological assays**, Haralambos Tzoupis, Georgios Leonis, Aggelos Avramopoulos, Heribert Reis, Żaneta Czyżnikowska, Sofia Zerva, Niki Vergadou, Loukas D. Peristeras, Konstantinos D. Papavasileiou, Michael N. Alexis, Thomas Mavromoustakos, Manthos G. Papadopoulos [National Hellenic Research Foundation]

See Applications / Medicinal Chemistry and Drug Design.

- 150-156 **Vector representation and its application of DNA sequences based on nucleotide triplet codons**, FengLan Bai, JiHong Zhang [Dalian Jiaotong University], JunSheng Zheng, Chao Li, LiWei Liu

Compared with single nucleotide, nucleotide triplet appears to contain more biological and genetic information, so it has been applied widely. We propose a new 3D-vector representation method of DNA sequences, namely use molecular weight of nucleotide triplet to define the '0' molecular plane, then make the 3-D coordinate transformation to map a DNA sequence into a curve by the coordinate accumulation, and then extract the D/D matrix's eigenvalues to describe, compare and analyze the DNA sequences as the numerical characterization.

- 157-164 **Comparative investigation of thermal and mechanical properties of cross-linked epoxy polymers with different curing agents by molecular dynamics simulation**, F. Jeyranpour, Gh. Alahyarizadeh [Islamic Azad University, Tehran], B. Arab

Molecular dynamics (MD) simulations were carried out to predict the thermal and mechanical properties of the cross-linked epoxy system composed of DGEBA resin and the curing agent TETA. To investigate the effects of curing agents, a comprehensive and comparative study was also performed on the thermal and mechanical properties of DGEBA/TETA and DGEBA/DETDA epoxy systems such as density, glass transition temperature (T_g), coefficient of thermal expansion (CTE) and elastic properties of different cross-linking densities and different temperatures.

- 165-173 **Brownian dynamics simulation of amphiphilic block copolymers with different tail lengths, comparison with theory and micelles**, Mohammad-Javad Hafezi, Farhad Sharif [Amirkabir University of Technology]

Study on the effect of amphiphilic copolymers structure on their self assembly is an interesting subject, with important applications in the area of drug delivery and biological system treatments. Brownian dynamics simulations were performed to study self-assembly of the linear amphiphilic block copolymers with the same hydrophilic head, but hydrophobic tails of different lengths.

- 174-180 **Visualizing potential energy curves and conformations on ultra high-resolution display walls**, Karl N. Kirschner [Bonn-Rhein-Sieg University of Applied Sciences], Dirk Reith, Oliver Jato, André Hinkenjann

In this contribution, we examine how visualization on an ultra high-resolution display wall can augment force-field research in the field of molecular modeling. Accurate force fields are essential for producing reliable simulations, and subsequently important for several fields of applications (e.g. rational drug design and biomolecular modeling). We discuss how using HORNET, a recently constructed specific ultra high-

resolution tiled display wall, enhances the visual analytics that are necessary for conformational-based interpretation of the raw data from molecular calculations.

- 181-189 **Development of quantitative structure activity relationships for the binding affinity of methoxypyridinium cations for human acetylcholinesterase**, Jason A. Morrill [University of Iowa], Joseph J. Topczewski, Alexander M. Lodge, Nilanthi Yasapala, Daniel M. Quinn

See Methodology / QSAR.

- 190-201 **Development of quantitative structure property relationships for predicting the melting point of energetic materials**, Jason A. Morrill [William Jewell College], Edward F.C. Byrd

The accurate prediction of the melting temperature of organic compounds is a significant problem that has eluded researchers for many years. In this report the derivation of QSPRs to predict melting temperatures of energetic materials based on descriptors calculated using the AM1 semiempirical quantum mechanical method are described.

- 202-212 **Influence of the ionic liquid [C₄mpy][Tf₂N] on the structure of the miniprotein Trp-cage**, Joseph L. Baker, Jeffrey Furbish, Gerrick E. Lindberg [Northern Arizona University]

We examine the effect of the ionic liquid [C₄mpy][Tf₂N] on the structure of the miniprotein Trp-cage and contrast these results with the behavior of Trp-cage in water. We find the ionic liquid has a dramatic effect on Trp-cage, though many similarities with aqueous Trp-cage are observed.

- 213-225 **Evaluation of novel Akt1 inhibitors as anticancer agents using virtual co-crystallized pharmacophore generation**, Mahmoud A. Al-Sha'er [Zarqa University], Iman Mansi, Inas Almazari, Nancy Hakooz

See Applications / Medicinal Chemistry and Drug Design.

- 226-234 **A structural insight into the inhibitory mechanism of an orally active PI3K/mTOR dual inhibitor, PKI-179 using computational approaches**, Mohd Rehan [King Abdulaziz University]

See Methodology / Ligand Docking.

- 235-244 **Structure-based de novo design, molecular docking and molecular dynamics of primaquine analogues acting as quinone reductase II inhibitors**, Erika Murce, Teobaldo Ricardo Cuya-Guizado, Helmut Isaac Padilla-Chavarria, Tanos Celmar Costa França, Andre Silva Pimentel [Pontifícia Universidade Católica do Rio de Janeiro]

See Applications / Medicinal Chemistry and Drug Design.

- 245-252 **PKR-inhibitor binds efficiently with human microtubule affinity-regulating kinase 4**, Farha Naz, Mohd. Shahbaaz, Shama Khan, Krishna Bisetty, Asimul Islam, Faizan Ahmad, Md. Imtaiyaz Hassan [Jamia Millia Islamia, Jamia Nagar]

See Methodology / Ligand Docking.

- 253-261 **Vienna Soil-Organic-Matter Modeler—Generating condensed-phase models of humic substances**, Axel Sündermann, Roland Solc, Daniel Tunega, Georg Haberhauer, Martin H. Gerzabek, Chris Oostenbrink [University of Natural Resources and Life Sciences Vienna]

Humic substances are ubiquitous in the environment and have manifold functions. While their composition is well known, information on the chemical structure and three-dimensional conformation is scarce. Here we describe the Vienna Soil-Organic-Matter Modeler, which is an online tool to generate condensed phase computer models of humic substances (<http://somm.boku.ac.at>).

- 262-275 **A ligand-entry surface of the nuclear receptor superfamily consists of the helix H3 of the ligand-binding domain**, Motonori Tsuji [Institute of Molecular Function, 2-105-14 Takasu]

See Applications / Ligand Binding.

- 276-282 **Binding site identification and role of permanent water molecule of PIM-3 kinase: A molecular dynamics study**, Zaheer Ul-Haq [University of Karachi], Sana Gul, Saman Usmani, Abdul Wadood, Waqasuddin Khan

See Applications / Enzyme Catalysis.

- 283-293 **In silico and experimental validation of protein–protein interactions between PknI and Rv2159c from Mycobacterium tuberculosis**, Arunkumar Venkatesan, Sameer Hassan, Kannan Palaniyandi, Sujatha Narayanan [National Institute for Research in Tuberculosis, Chennai]

See Applications / Protein - Protein Interactions.

- 294-302 **Insight into the relationship between structure and magnetic properties in icosahedral Fe_nPt_{55-n} (n = 0–55) nanoparticles: DFT approach**, Minghua Zhang, Ning Wang, Yongpeng Yang, Shiping Huang [Beijing University of Chemical Technology]

Structural, electronic and magnetic properties of Fe_nPt_{55-n} nanoparticles have been systematically studied based on the density functional theory. Firstly, the results show that surface Fe fraction has the same change tendency with excess energy and the nanoparticles have high stability when surface Fe fraction is small and excess energy is low.

- 303-318 **Case-specific performance of MM-PBSA, MM-GBSA, and SIE in virtual screening**, Salla I. Virtanen, Sanna P. Niinivehmas, Olli T. Pentikäinen [University of Jyväskylä]

In drug discovery the reliable prediction of binding free energies is of crucial importance. Methods that combine molecular mechanics force fields with continuum solvent models have become popular because of their high accuracy and relatively good computational efficiency. In this research we studied the performance of molecular mechanics generalized Born surface area (MM-GBSA), molecular mechanics Poisson–Boltzmann surface area (MM-PBSA), and solvated interaction energy (SIE) both in their virtual screening efficiency and their ability to predict experimentally determined binding affinities for five different protein targets.

- 319-324 **Rational design of a carboxylic esterase RhEst1 based on computational analysis of substrate binding**, Qi Chen, Zheng-Jiao Luan, Hui-Lei Yu, Xiaolin Cheng, Jian-He Xu [East China University of Science and Technology]

See Applications / Enzyme Catalysis.

- 325-341 **An ab initio molecular dynamics analysis of lignin as a potential antioxidant for hydrocarbons**, Tongyan Pan, Cheng Cheng [Illinois Institute of Technology]

See Applications / Medicinal Chemistry and Drug Design.

- 342-361 **Homology modeling of parasite histone deacetylases to guide the structure-based design of selective inhibitors**, Jelena Melesina, Dina Robaa, Raymond J. Pierce, Christophe Romier, Wolfgang Sippl [Martin-Luther-Universität Halle-Wittenberg]

See Applications / Homology Modeling.

Journal of Computational Chemistry, 36 (30), November, 2015.

- 2209–2218 **Assessment and acceleration of binding energy calculations for protein–ligand complexes by the fragment molecular orbital method**, Takao Otsuka, Noriaki Okimoto [RIKEN Quantitative Biology Center] and Makoto Taiji

See Applications / Membrane Proteins and Lipid peptide interactions.

- 2219–2227 **Ab Initio spectroscopic characterization of borane, BH, in its $X^1\Sigma^+$ electronic state**, Jacek Koput [Adam Mickiewicz University]

The accurate potential energy and electric dipole moment functions of borane, BH, in its $X^1\Sigma^+$ electronic state have been determined from ab initio calculations using the multireference averaged coupled-pair functional method in conjunction with the correlation-consistent core-valence basis sets up to septuple-zeta quality.

- 2228–2235 **Thiol versus hydroxamate as zinc binding group in HDAC inhibition: An Ab initio QM/MM molecular dynamics study**, Wenjing Gong, Ruibo Wu and Yingkai Zhang [New York University, New York]

See Methodology / Ligand Docking.

- 2236–2245 **Multiparticle moves in acceptance rate optimized monte carlo**, Tobias Neumann, Denis Danilov and Wolfgang Wenzel [Karlsruhe Institute of Technology]

Molecular Dynamics (MD) and Monte Carlo (MC) based simulation methods are widely used to investigate molecular and nanoscale structures and processes. In this work, we discuss a multiparticle Acceptance Rate Optimized Monte Carlo approach (AROMoCa) to construct collective moves with near unit acceptance probability, while preserving detailed balance even for large step sizes.

- 2246–2259 **A new extension of the polarizable continuum model: Toward a quantum chemical description of chemical reactions at extreme high pressure**, Roberto Cammi [Università di Parma, Parma]

A quantum chemical method for studying potential energy surfaces of reactive molecular systems at extreme high pressures is presented. The method is an extension of the standard Polarizable Continuum Model that is usually used for Quantum Chemical study of chemical reactions at a standard condition of pressure.

- 2260–2269 **Water solvent effects using continuum and discrete models: The nitromethane molecule, CH₃NO₂**, Lucas Modesto-Costa, Elmar Uhl and Itamar Borges Jr [Instituto Militar De Engenharia]

The first three valence transitions of the two nitromethane conformers (CH₃NO₂) are two dark $n \rightarrow \pi^*$ transitions and a very intense $\pi \rightarrow \pi^*$ transition. In this work, these transitions in gas-phase and solvated in water of both conformers were investigated theoretically.

Journal of Computational Chemistry, 36 (31), December, 2015.

- 2271–2290 **Analytical gradients for MP2, double hybrid functionals, and TD-DFT with polarizable embedding described by fluctuating charges**, Ivan Carnimeo, Chiara Cappelli and Vincenzo Barone [Scuola Normale Superiore]

A polarizable quantum mechanics (QM)/ molecular mechanics (MM) approach recently developed for Hartree–Fock (HF) and Kohn–Sham (KS) methods has been extended to energies and analytical gradients for MP2, double hybrid functionals, and TD-DFT models, thus allowing the computation of equilibrium structures for excited electronic states together with more accurate results for ground electronic states.

- 2291–2301 **Low-energy structures of benzene clusters with a novel accurate potential surface**, M. Bartolomei, F. Pirani and J. M. C. Marques [Universidade de Coimbra]

The benzene-benzene (Bz-Bz) interaction is present in several chemical systems and it is known to be crucial in understanding the specificity of important biological phenomena. In this work, we propose a novel Bz-Bz analytical potential energy surface which is fine-tuned on accurate ab initio calculations in order to improve its reliability.

- 2302–2316 **Ion strength limit of computed excess functions based on the linearized Poisson–Boltzmann equation**, Dan Fraenkel [Eltron Research & Development Inc.]

The linearized Poisson–Boltzmann (L-PB) equation is examined for its κ -range of validity (κ , Debye reciprocal length). This is done for the Debye–Hückel (DH) theory, i.e., using a single ion size, and for the SiS treatment (D. Fraenkel, Mol. Phys. **2010**, 108, 1435), which extends the DH theory to the case of ion-size dissimilarity (therefore dubbed DH–SiS).

- 2317–2327 **DSPMP: Discriminating secretory proteins of malaria parasite by hybridizing different descriptors of Chou's pseudo amino acid patterns**, Guo-Liang Fan [Inner Mongolia University, Hohhot], Xiao-Yan Zhang, Yan-Ling Liu, Yi Nang and Hui Wang

Identification of the proteins secreted by the malaria parasite is important for developing effective drugs and vaccines against infection. Therefore, we developed an improved predictor called “DSPMP” (Discriminating Secretory Proteins of Malaria Parasite) to identify the secretory proteins of the malaria parasite by integrating

several vector features using support vector machine-based methods. DSPMP achieved an overall predictive accuracy of 98.61%, which is superior to that of the existing predictors in this field.

- 2328–2343 **Hexahalogenated and their mixed benzene derivatives as prototypes for the understanding of halogen···halogen intramolecular interactions: New insights from combined DFT, QTAIM-, and RDG-based NCI analyses**, Pradeep R. Varadwaj [National Taiwan University], Arpita Varadwaj and Bih-Yaw Jin

A large number of fully halogenated benzene derivatives containing the fluorine, chlorine, bromine, and iodine atoms have been experimentally synthesized both as single- and co-crystals (e.g., Desiraju et al., Chem. Eur. J. 2006, 12, 2222), yet the natures of the halogen ··· halogen interactions between the vicinal halogens in these compounds within the intramolecular domain are undisclosed. We present here our newly discovered theoretical results that delineate whilst the nature of an F···F interaction in a pair of two adjacent fluorine atoms in either of the hexafluorobenzene and 1,4-dibromotetrafluorobenzene compounds.

- 2344–2349 **Simulated tempering based on global balance or detailed balance conditions: Suwa–Todo, heat bath, and Metropolis algorithms**, Yoshiharu Mori and Hisashi Okumura [Institute for Molecular Science]

Simulated tempering (ST) is a useful method to enhance sampling of molecular simulations. When ST is used, the Metropolis algorithm, which satisfies the detailed balance condition, is usually applied to calculate the transition probability. Recently, an alternative method that satisfies the global balance condition instead of the detailed balance condition has been proposed by Suwa and Todo. In this study, ST method with the Suwa–Todo algorithm is proposed. Molecular dynamics simulations with ST are performed with three algorithms (the Metropolis, heat bath, and Suwa–Todo algorithms) to calculate the transition probability.

Journal of Molecular Modeling, 21 (12), December, 2015.

- 311 **Theoretical study on alkali-metal doped N₃H₃ complexes: an in-depth understanding of the origin of electride and alkalide and their large nonlinear optical properties**, Wan-Ming Liang, Zeng-Xia Zhao, Di Wu, Wei-Ming Sun, Ying Li [Jilin University], Zhi-Ru Li

By doping the model complexant N₃H₃ with one or two lithium atoms, the geometrical and electronic structures as well as static electric properties of the resulting Li(N₃H₃), (N₃H₃)Li⁺ and Li(N₃H₃)Li⁺ complexes can be explored using the B3LYP, BHandHLYP, CAM-B3LYP and MP2 methods. All three complexes, especially Li(N₃H₃), were found to have large first hyperpolarizabilities (β_0). Meanwhile, Li(N₃H₃) and Li(N₃H₃)Li⁺ exhibited electride and alkalide characteristics, respectively.

- 310 **Functional insights from a comparative study on the dynamics of Antigen85 proteins and MPT51 from Mycobacterium tuberculosis**, Shobana Sundar, David Annaraj, Anitha Selvan, Pallavi Guha Biswas, Reshma Vijayakumaran, Sharmila Anishetty [Anna University, Chennai]

See Applications / Medicinal Chemistry and Drug Design.

- 309 **Product rotational angular momentum polarization of H + FCl ($v=0-5$; $j=0, 3, 6, 9$) → HF + Cl and HCl + F at $E_{\text{rel}}=0.5-20$ kcal mol⁻¹**, Victor Wei-Keh Chao (Wu) [National Kaohsiung University of Applied Sciences]

The rotational angular momentum polarizations of product molecules of the title reactions on the ground potential energy surface $1^2A'$ of DHTSN [Deskevich et al. *J Chem Phys* 2006, **124**, 224303] have been studied using the quasi-classical trajectory method.

- 308 **An investigation of folic acid–protein association sites and the effect of this association on folic acid self-assembly**, Rajat Gupta, Prasanta Kalita, Omkar Patil, Sanat Mohanty [Indian Institute of Technology Delhi]

See Applications / Protein Dynamics.

- 307 **The antiradical activity of some selected flavones and flavonols. Experimental and quantum mechanical study**, Zbigniew Sroka [Wrocław Medical University], Beata Żbikowska, Jerzy Hładyszowski

The aim of the study was to examine the antiradical and antioxidant activity of some flavones and flavonols with different models of hydroxylation and methoxylation. Antiradical activity was measured using ABTS and DPPH radicals and ferric ions (FRAP test).

- 305 **Nonlinear optical behavior of Li_nF ($n=2-5$) superalkali clusters**, Ambrish Kumar Srivastava, Neeraj Misra [University of Lucknow, Lucknow]

Hyperlithiated clusters are known for their unusual bonding characteristics and lower ionization potentials. This study reports nonlinear optical (NLO) properties of a series of hyperlithiated clusters, Li_nF ($n=2-5$) for the first time.

- 304 **Pressure-induced phase transition in CrO_2** , Sebahaddin Alptekin [Çankırı Karatekin University]

The ab initio constant pressure molecular dynamics technique and density functional theory with generalized gradient approximation (GGA) was used to study the pressure-induced phase transition of CrO_2 .

- 303 **Study on electronic structures and properties of neutral and charged arsenic sulfides $[As_nS_3^{(-1,0,+1)}, n=1-6]$ with the Gaussian-3 scheme**, Bin Liu, Jucai Yang [Inner Mongolia University of Technology]

The structures and energies of neutral and charged arsenic sulfides $As_nS_3^{(-1,0,+1)}$ ($n=1-6$) were studied systematically with the G3 method. The ground-state structures of these species are reported.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

A. Cesàro
cesaro@units.it
Lab. of Physical and
Macromolecular Chemistry,
Department of Chemical and
Pharmaceutical Sciences,
University of Trieste, via L.
Giorgieri 1,
34127 Trieste, Italy

A. Y. Lizunov
al_bio@mail.ru
Department of Mathematics,
Moscow Institute of Physics and
Technology,
Moscow 117303, Russia

Adelene Y. L. Sim
adelenes@bii.a-star.edu.sg
Bioinformatics Institute,
Agency for Science, Technology,
and Research,
30 Biopolis Street, Matrix,
#07-01, Singapore 138671

Adrian G. Turjanski
adrian@qi.fcen.uba.ar
Departamento de Química
Biológica,
Facultad de Ciencias Exactas y
Naturales,
Universidad de Buenos Aires,
Ciudad Universitaria, Pabellón II,
C1428EHA,
Ciudad de Buenos Aires, Argentina

Akio Kitao
kitao@iam.u-tokyo.ac.jp
Center for Computational Sciences,
University of Tsukuba, 1-1-1
Tennodai,
Tsukuba, Ibaraki 305-8571, Japan

Aleksey V. Zima
azima@luc.edu
Department of Cell and Molecular
Physiology,
Loyola University Chicago,
Stritch School of Medicine,
Maywood, Illinois

Alessandra Magistrato
alessandra.magistrato@sissa.it
CNR-IOM-Democritos National
Simulation Center
c/o International School for
Advanced Studies (SISSA/ISAS),

via Bonomea 265, Trieste, Trieste,
Italy

Andre Silva Pimentel
a_pimentel@puc-rio.br
Departamento de Química,
Pontificia Universidade Católica do
Rio de Janeiro,
RJ 22453-900, Brazil

Angel E. García
agarcia@lanl.gov
Center for Biotechnology and
Interdisciplinary Studies,
Rensselaer Polytechnic Institute,
Troy, New York

António M. Baptista
baptista@itqb.unl.pt
Instituto de Tecnologia Química e
Biológica António Xavier,
Universidade Nova de Lisboa, Av.
da República,
2780-157 Oeiras, Portuga

B. D. Marsden
brian.marsden@sgc.ox.ac.uk
SGC, Nuffield Department of
Medicine,
University of Oxford,
Old Road Campus Research
Building,
Roosevelt Drive, Headington,
Oxford, OX3 7DQ, UK

Bin Liu
bliu@insun.hit.edu.cn
Key Laboratory of Network
Oriented Intelligent Computation,
Harbin Institute of Technology
Shenzhen Graduate School,
Shenzhen, Guangdong 518055,
China

Cheng Cheng
ccheng20@hawk.iit.edu
Department of Civil, Architectural
and Environmental Engineering,
Illinois Institute of Technology,
3201 S. Dearborn St. Alumni
Memorial Hall 215,
Chicago, IL 60616, United States

Cheng Luo
cluo@simm.ac.cn
Drug Discovery and Design
Center,
State Key Laboratory of Drug
Research,
Shanghai Institute of Materia
Medica,
Chinese Academy of Sciences,
Shanghai 201203, China

Chia-Ning Yang

cnyang@nuk.edu.tw
Department of Life Sciences,
National University of Kaohsiung,
Kaohsiung, Taiwan

Chris Oostenbrink
chris.oostenbrink@boku.ac.at
Department of Material Sciences
and Process Engineering,
Institute of Molecular Modeling
and Simulation,
University of Natural Resources
and Life Sciences Vienna,
Muthgasse 18, A-1190 Vienna,
Austria

Claire A. Lemarchand
clairel@ruc.dk
DNRF Centre "Glass and Time",
IMFUA,
Department of Sciences,
Roskilde University,
Universitetsvej 1,
Postbox 260, DK-4000 Roskilde,
Denmark

Clifford E. Woodward
c.woodward@adfa.edu.au
School of Physical, Environmental
and Mathematical Sciences,
University of New South Wales,
Canberra ACT 2600, Australia

Dan Fraenkel
dfraenkel@eltronresearch.com
Eltron Research & Development
Inc.,
Boulder, Colorado

David L. Mobley
dmobley@uci.edu
Department of Pharmaceutical
Sciences,
University of California, Irvine,
147 Bison Modular, Irvine,
CA, 92697, USA

David P. Fairlie
d.fairlie@imb.uq.edu.au
Division of Chemistry and
Structural Biology,
Institute for Molecular Bioscience,
The University of Queensland,
Brisbane,
Queensland 4072, Australia

David R. Liu
drlui@fas.harvard.edu
Department of Chemistry &
Chemical Biology,
Harvard University, 12 Oxford
Street,
Cambridge, Massachusetts 02138,
United States

Didier Mathieu
didier.mathieu@cea.fr
CEA, DAM, Le Ripault,
F-37260 Monts, France

Elaheh K. Goharshadi
gohari@um.ac.ir
Dept. of Chemistry,
Ferdowsi University of Mashhad,
Mashhad 91779, Iran

Elena Rosini
elena.rosini@uninsubria.it
Dipartimento di Biotecnologie e
Scienze della Vita,
Università degli studi dell'Insubria,
via J. H. Dunant 3, 21100 Varese,
Italy

Emanuel Schneck
schneck@mpikg.mpg.de
Biomaterials Department,
Max Planck Institute of Colloids
and Interfaces,
D-14476 Potsdam, Germany

Emil Alexov
ealexov@clemson.edu
Department of Physics,
Computational Biophysics and
Bioinformatics,
Clemson University, Clemson, SC
29634.

Emilia A. Lubecka
emilial@chem.univ.gda.pl
Faculty of Chemistry,
University of Gdańsk,
Wita Stwosza 63, 80-308,
Gdańsk, Poland

Esteban Vöhringer-Martinez
evohringer@udec.cl
Departamento de Físico Química,
Facultad de Ciencias Químicas,
Universidad de Concepción,
Milenium Nucleus Chemical
Processes and Catalysis,
Concepción, Chile

Farhad Sharif
sharif@aut.ac.ir
Department of Polymer
Engineering and Color
Technology,
Amirkabir University of
Technology,
424Hafez Avenue, Tehran, Iran

Fernanda Borges
fborges@fc.up.pt
CIQUP/Departamento de Química
e Bioquímica,
Faculdade de Ciências,
Universidade do Porto,

Porto 4169-007, Portugal

Frank Jensen
frj@chem.au.dk
Department of Chemistry,
Aarhus University, Aarhus,
Denmark

Frank Noé
frank.noe@fu-berlin.de
Department for Mathematics and
Computer Science,
Freie Universität, Arnimallee 6,
Berlin 14195, Germany

Gabriele Cruciani
gabri@chemiome.chm.unipg.it
Department of Chemistry,
Biology and Biotechnology,
University of Perugia,
Via Elce di Sotto 8,
06123 Perugia, Italy

Gerrick E. Lindberg
gerrick.lindberg@nau.edu
Department of Chemistry and
Biochemistry,
Northern Arizona University,
700 S. Osbourne Drive, Flagstaff,
AZ 86011, United States

Gh. Alahyarizadeh
g_alahyarizadeh@yahoo.com
Department of Mechanical
Engineering,
Faculty of Engineering,
North Tehran Branch,
Islamic Azad University,
Tehran, Iran

Gianni De Fabritiis
gianni.defabritiis@upf.edu
Computational Biophysics
Laboratory (GRIB-IMIM),
Universitat Pompeu Fabra,
Barcelona Biomedical Research
Park (PRBB),
Doctor Aiguader 88, 08003
Barcelona,
Barcelona, Spain

Guo-Liang Fan
eeguoliangfan@sina.com
Department of Physics,
School of Physical Science and
Technology,
Inner Mongolia University,
Hohhot, China

Gábor Czirják
czirjak.gabor@med.semmelweis-
univ.hu
Department of Physiology,
Semmelweis University, P.O. Box
259,
H-1444 Budapest, Hungary

Hai-Long An
hailong_an@hebut.edu.cn

Key laboratory of Molecular
Biophysics,
Tianjin, Hebei Province, China

Hanoch Senderowitz
hsenderowitz@gmail.com
Department of Chemistry,
Bar Ilan University,
Ramat-Gan 52900, Israel

Haojun Liang
hjliliang@ustc.edu.cn
CAS Key Laboratory of Soft
Matter Chemistry,
iChEM (Collaborative Innovation
Center of Chemistry for Energy
Materials),
Department of Polymer Science
and Engineering,
National Synchrotron Radiation
Laboratory,
University of Science and
Technology of China,
Hefei, Anhui 230026, P. R. China

Hisashi Okumura
hokumura@ims.ac.jp
Research Center for Computational
Science,
Institute for Molecular Science,
Okazaki, Aichi, Japan

Irene T. Weber
iweber@gsu.edu
Department of Biology,
Georgia State University,
Atlanta, GA 30303, USA

Itamar Borges Jr
itamar@ime.eb.br
Departamento De Química,
Instituto Militar De Engenharia,
Rio De Janeiro, Brazil

J. M. C. Marques
qtmarque@ci.uc.pt
Departamento de Química,
Universidade de Coimbra,
Coimbra, Portugal

Jacek Koput
koput@amu.edu.pl
Department of Chemistry,
Adam Mickiewicz University,
Poznań, Poland

Jane R Hanrahan
jane.hanrahan@sydney.edu.au
Faculty of Pharmacy,
University of Sydney, Sydney,
NSW 2006, Australia

Jaroslav Polanski
polanski@us.edu.pl
Institute of Chemistry, University
of Silesia,
9 Szkolna Street, 40-006 Katowice,
Poland

Jason A. Morrill
morrillj@william.jewell.edu
Department of Chemistry,
University of Iowa, E331
Chemistry Building,
Iowa City, IA 52242-1294, United
States

Jason A. Morrill
morrillj@william.jewell.edu
Department of Chemistry,
William Jewell College,
500 College Hill, Liberty,
MO 64068, USA

Jeetain Mittal
jeetain@lehigh.edu
Department of Chemical and
Biomolecular Engineering,
Lehigh University, Bethlehem,
Pennsylvania 18015, United States

Jerry Tsai
jtsai@pacific.edu
Department of Chemistry,
University of the Pacific,
3601 Pacific Avenue,
Stockton, CA 95219

JiHong Zhang
iamzjh@126.com
School of Science,
Dalian Jiaotong University,
Dalian 116028, China

Jian-He Xu
jianhexu@ecust.edu.cn
State Key Laboratory of Bioreactor
Engineering,
East China University of Science
and Technology,
Shanghai, China

Ju-Guang Han
jghan@ustc.edu.cn
National Synchrotron Radiation
Laboratory,
University of Science and
Technology of China,
Hefei 230029, People's Republic of
China.

Juan Rodrigo Salazar
juan.salazar@ulsa.mx
Facultad de Ciencias Químicas,
Universidad La Salle,
Benjamin Franklin 47,
06140 México City, Mexico

Jucai Yang
yangjc@imut.edu.cn
Department of Environmental
Science and Engineering,
Inner Mongolia University of
Technology,
Hohhot, 010051, Peoples Republic
of China

K. N. Houk

houk@chem.ucla.edu
Department of Chemical and
Biomolecular Engineering,
University of California, Los
Angeles,
California 90095, United States

Karl N. Kirschner
karl.kirschner@h-brs.de
Bonn-Rhein-Sieg University of
Applied Sciences,
Grantham-Allee 20,
54757 Sankt Augustin, Germany

Katrin Weise
katrin.weise@tu-dortmund.de
Physical Chemistry I - Biophysical
Chemistry,
TU Dortmund University,
Dortmund,
Germany

Khaled H. Barakat
kbarakat@ualberta.ca
Faculty of Pharmacy and
Pharmaceutical Sciences,
University of Alberta,
Edmonton, AB, Canada

M. Neek-Amal
mehdi.neekamal@gmail.com
Department of Physics,
Science and Research Branch,
Islamic Azad University,
Tehran, Iran

M. Teresa Pisabarro
mayte@biotec.tu-dresden.de
Structural Bioinformatics,
BIOTEC,
TU Dresden, Tatzberg 47-51,
01307 Dresden, Germany

Mahmoud A. Al-Sha'er
a.mahmoud@zu.edu.jo
Faculty of Pharmacy,
Zarqa University, P.O.Box 132222,
Zarqa, 13132, Jordan

Manthos G. Papadopoulos
mpapad@eie.gr
Institute of Biology,
Pharmaceutical Chemistry and
Biotechnology,
National Hellenic Research
Foundation,
48 Vas. Constantinou Ave.,
Athens 11635, Greece

Marco Bocola
m.bocola@biotec.rwth-aachen.de
Chair of Biotechnology,
RWTH Aachen University,
Worringer Weg 3, 52074,
Aachen, Germany

Mark Gerstein
mark.gerstein@yale.edu
Department of Computer Science,

Yale University, New Haven,
CT 06511, USA

Mark P. Waller
m.waller@uni-muenster.de
Theoretical Chemistry, Organic
Chemistry Institute,
Westfälische Wilhelms Universität
Münster,
Correnstrasse 40, Münster, 48149,
Germany

Matthias Rarey
rarey@zbh.uni-hamburg.de
University of Hamburg, Center for
Bioinformatics,
Research Group for Computational
Molecular Design,
Bundesstraße 43, 20146 Hamburg,
Germany

Md. Imtaiyaz Hassan
mihassan@jmi.ac.in
Center for Interdisciplinary
Research in Basic Sciences,
Jamia Millia Islamia, Jamia Nagar,
New Delhi 110025, India

Michal Linial
michall@cc.huji.ac.il
Department of Biological
Chemistry,
Institute of Life Sciences,
The Edmond J. Safra Campus,
The Hebrew University of
Jerusalem,
Givat Ram, 91904, Israel

Mohd Rehan
mrehan786@gmail.com
King Fahd Medical Research
Center,
King Abdulaziz University,
Jeddah 21589, Saudi Arabia

Molly Hammell
mhammell@cshl.edu
Cold Spring Harbor Laboratory,
Cold Spring Harbor, NY, 11724,
USA

Motonori Tsuji
motonori@molfuction.com
Institute of Molecular Function,
2-105-14 Takasu, Misato-shi,
Saitama 341-0037, Japan

Motonori Tsuji
motonori@molfuction.com
Institute of Molecular Function,
2-105-14 Takasu, Misato-shi,
Saitama, 341-0037, Japan

Mustafa Tekpinar
tekpinar@buffalo.edu
Department of Physics, Faculty of
Science,
Yüzüncü Yıl University, 65100,
Van, Turkey

Neeraj Misra
neerajmisra11@gmail.com
Department of Physics,
University of Lucknow, Lucknow,
226007, Uttar Pradesh, India

Nor Hadiani Ismail
norhadiani@puncakalam.uitm.edu.
my
Atta-ur-Rahman Institute for
Natural Product Discovery,
Universiti Teknologi MARA,
Puncak Alam Campus, 42300,
Selangor D.E., Malaysia

Noriaki Okimoto
okimoto@riken.jp
Laboratory for Computational
Molecular Design,
Computational Biology Research
Core,
RIKEN Quantitative Biology
Center (QBiC),
Hyogo, Japan

Olli T. Pentikäinen
olli.t.pentikainen@jyu.fi
Department of Biological and
Environmental Science &
Nanoscience Center,
University of Jyväskylä, P.O. Box
35,
40014, University of Jyväskylä,
Finland

Paloma Ballesteros
pballesteros@ccia.uned.es
Laboratory of Organic Synthesis
and
Molecular Imaging by Magnetic
Resonance,
Faculty of Sciences, UNED,
28040 Madrid, Spain

Parbati Biswas
pbiswas@chemistry.du.ac.in
Department of Chemistry,
University of Delhi,
Delhi 110007, India

Pradeep R. Varadwaj
pradeep@t.okayama-uc.jp
Department of Chemistry,
National Taiwan University,
Taipei, Taiwan

Qingwen Zhang
zqw@sus.edu.cn
College of Physical Education and
Training,
Shanghai University of Sport,
399 Chang Hai Road,
Shanghai 200438, China

Ramesh Chandra Deka
ramesh@tezu.ernet.in
Department of Chemical Sciences,
Tezpur University, Napaam,

Tezpur 784028, Assam, India

Ray Luo
ray.luo@uci.edu
Chemical Physics and Materials
Physics Graduate Program,
University of California, Irvine,
California 92697, United States

Richard Lavery
richard.lavery@ibcp.fr
BMSSI, UMR 5086 CNRS/Univ.
Lyon I,
Institut de Biologie et Chimie des
Protéines,
7 passage du Vercors, Lyon 69367,
France

Robert B. Best
robertbe@helix.nih.gov
Laboratory of Chemical Physics,
National Institute of Diabetes and
Digestive and Kidney Diseases,
National Institutes of Health,
Bethesda, MD 20892

Robert B. Best
robertbe@helix.nih.gov
Laboratory of Chemical Physics,
National Institute of Diabetes and
Digestive and Kidney Diseases,
National Institutes of Health,
Bethesda,
Maryland 20892, United States

Roberto Cammi
roberto.cammi@unipr.it
Dipartimento di Chimica,
Università di Parma, Parma, Italy

Ron Elbe
ron@ices.utexas.edu
Institute for Computational
Engineering and Sciences,
University of Texas at Austin,
Austin, Texas

S. Banu Ozkan
banu.ozkan@asu.edu
Department of Physics and Center
for Biological Physics,
Arizona State University, Tempe,
AZ.

Sanat Mohanty
sanat.mohanty@gmail.com
Department of Chemical
Engineering,
Indian Institute of Technology
Delhi,
New Delhi, India, 110016

Sarah Rauscher
sarah.rauscher@mpibpc.mpg.de
Department of Theoretical and
Computational Biophysics,
Max Planck Institute for
Biophysical Chemistry,
Göttingen 37077, Germany

Sebahaddin Alptekin
salptekin@karatekin.edu.tr
Department of Physics, Faculty of
Science,
Çankırı Karatekin University,
18100, Çankırı, Turkey

Sergei Grudinin
Sergei.Grudinin@inria.fr
Université Grenoble Alpes,
Laboratoire Jean Kuntzmann
(LJK),
F-38000 Grenoble, France

Sharmila Anishetty
sharmi.anishetty@gmail.com
Centre for Biotechnology,
Anna University, Chennai,
600025, India

Shikha Nangia
snangia@syr.edu
Department of Biomedical and
Chemical Engineering,
Syracuse University, Syracuse,
New York 13244, United States

Shipping Huang
huangsp@mail.buct.edu.cn
State Key Laboratory of Organic-
Inorganic Composites,
Beijing University of Chemical
Technology,
Beijing 100029, China

SonBinh T. Nguyen
stn@northwestern.edu
Department of Chemistry and
International Institute for
Nanotechnology,
Northwestern University, 2145
Sheridan Road,
Evanston, Illinois 60208, United
States

Stephen R. Wassall
swassall@iupui.edu
Department of Physics,
Indiana University-Purdue
University Indianapolis,
Indianapolis, Indiana

Sujatha Narayanan
sujatha.sujatha36@gmail.com
Department of Immunology,
National Institute for Research in
Tuberculosis, #1,
Mayor Sathiyamoorthy Road,
Chetpet, Chennai 600 031, India

Sungwoo Hong
hongorg@kaist.ac.kr
Center for Catalytic Hydrocarbon
Functionalizations,
Institute of Basic Science (IBS),
Daejeon 305-701, Korea

Sutapa Mondal Roy

sutapa24@gmail.com
Department of Applied Chemistry,
S. V. National Institute of
Technology,
Surat 395007, India

Teobald Kupka
teobaldk@yahoo.com
University of Opole,
Faculty of Chemistry, 48,
Oleska Str., 45-052 Opole, Poland

Thomas E Cheatham, III
tec3@utah.edu
Department of Medicinal
Chemistry,
College of Pharmacy,
2000 East 30 South Skaggs 307,
The University of Utah, Salt Lake
City,
Utah 84112-5820, United States

Tusar Bandyopadhyay
btusar@barc.gov.in
Theoretical Chemistry Section,
Bhabha Atomic Research Centre,
Mumbai 400 085, India

Victor Wei-Keh Chao (Wu)
victorbres22de@yahoo.de
victorbres1g@gmail.com
Department of Chemical and
Materials Engineering,
National Kaohsiung University of
Applied Sciences,
No. 415, Chien Kung Road,
Sanmin District,
Kaohsiung, 80778, Taiwan,
Republic of China

Vincenzo Barone
vincenzo.barone@sns.it
Scuola Normale Superiore,
Pisa, Italy

Wagner B.De Almeida
wbdealmeida@gmail.com
Laboratório de Química
Computacional (LQC),
Departamento de Química
Inorgânica,
Instituto de Química,
Universidade Federal Fluminense,
Campus do Valonguinho, Centro,
Niterói,
RJ CEP: 24020-141, Brazil

Wenjun Zheng
wjzheng@buffalo.edu
239 Fronczak Hall,
Buffalo, NY 14260.

William J. Welsh
welshwj@rwjms.rutgers.edu
Department of Pharmacology,
Cancer Institute of New Jersey,
Rutgers University, Piscataway,
NJ, 08854, USA

Wolfgang Sippl
wolfgang.sippl@pharmazie.uni-
halle.de
Institute of Pharmacy,
Martin-Luther-Universität Halle-
Wittenberg,
Halle/Saale, Germany

Wolfgang Wenzel
wolfgang.wenzel@kit.edu
Institute of Nanotechnology,
Karlsruhe Institute of Technology,
Karlsruhe, Germany

Yaakov Levy
koby.levy@weizmann.ac.il
Department of Structural Biology,
Weizmann Institute of Science,
Rehovot 76100, Israel

Yi Qin Gao
gaoyq@pku.edu.cn
Biodynamic Optical Imaging
Center (BIOPIC),
School of Life Sciences,
College of Chemistry and
Molecular Engineering,
Peking University, Beijing 100871,
China

Ying Li
liyingedu@jlu.edu.cn
Institute of Theoretical Chemistry,
Jilin University, Changchun,
130023,
People's Republic of China

Yingkai Zhang
yingkai.zhang@nyu.edu
Department of Chemistry,
New York University, New York,
New York

Yuji Sugita
sugita@riken.jp
RIKEN Advanced Institute for
Computational Science,
6-7-1 minatojima-minamimachi,
Chuo-ku, Kobe, Hyogo 640-0047,
Japan

Yun-Dong Wu
wuyd@pkusz.edu.cn
Laboratory of Computational
Chemistry and Drug Design,
Laboratory of Chemical Genomics,
Peking University Shenzhen
Graduate School,
Shenzhen 518055, China

Zaheer Ul-Haq
zaheer.qasmi@iccs.edu
Dr Panjwani Center for Molecular
Medicine and Drug Research,
International Center for Chemical
and Biological Sciences,
University of Karachi,
Karachi 75270, Pakistan

Zbigniew Sroka
z.g.sroka@gmail.com
Department of Pharmacognosy,
Wrocław Medical University,
ul. Borowska 211, 50-556,
Wrocław, Poland

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Editor:

R.Mutyala.
MMCC Results
RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126

Tel. (858) 663-0162
E-mail: mmccresults@gmail.com

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.
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Anston Feenstra, Vrije Univ., Amsterdam, Netherlands
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